Enantioselective Synthesis of *gem*-Disubstituted *N*-Boc Diazaheterocycles via Decarboxylative Asymmetric Allylic Alkylation

Alexander W. Sun,‡ Stephan N. Hess,‡ and Brian M. Stoltz*

The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California, 91125, United States

Table of Contents

Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. *tert*-Butyl 3-oxopiperazine-1-carboxylate **1** was obtained from Combi-Blocks. Commercially obtained reagents were used as received. Chemicals were purchased from Sigma Aldrich/Strem/Alfa Aesar/Combi-Blocks and used as received.

Reaction temperatures were controlled by an IKAmag temperature modulator. Glove box manipulations were performed under a nitrogen atmosphere. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, iodine on silica, ninhydrin, or $KMnO_4$ staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040–0.063 mm) was used for flash chromatography.

Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing a Chiralpak IC column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 254 nm. Reverse Phase Preparatory HPLC was performed with a Teledyne ISCO ACCQPrep HP125 preparative liquid chromatography system equipped with a RediSep Prep C18 5 μm column (20 x 250 mm).

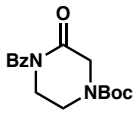
^{1}H NMR spectra were recorded on a Varian Inova 600 MHz or 500 MHz spectrometer or a Bruker Avance HD 400 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm) or CH_3OH (δ 3.31 ppm). ^{13}C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer or a Bruker Avance HD 400 MHz spectrometer and are reported relative to residual $CDCl_3$ (δ 77.16 ppm) or CD_3OD (δ 49.00 ppm). Data for ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). Some reported spectra include minor solvent impurities of water (δ 1.56 or 4.87 ppm), ethyl acetate (δ 4.12, 2.05, 1.26 ppm), methylene chloride (δ 5.30 ppm), acetone (δ 2.17 ppm), grease (δ 1.26, 0.86 ppm), and/or silicon grease (δ 0.07 ppm), which do not impact product assignments.

IR spectra were obtained using a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm pathlength cell and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent). Stereochemistry is assigned by analogy to previous results.[1]

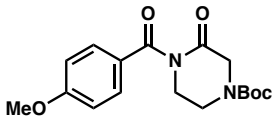
List of Abbreviations: An – Anisoyl, Boc – tert-Butyloxycarbonyl, BRSM – based on recovered starting material, Bz – benzoyl, CH_2Cl_2 – methylene chloride, Cbz – carboxybenzyl, ee – enantiomeric excess, Et_2O – diethyl ether, EtOAc – ethyl acetate, IPA – isopropanol, LHMDS – lithium hexamethyldisilazide, MeCN – acetonitrile, MeOH – methanol, SFC – supercritical fluid chromatography, THF – tetrahydrofuran, TFA – trifluoroacetic acid, TLC – thin-layer chromatography.

Preparation of Known Compounds: Allyl cyanoformate was prepared according to the method of Weber.[2] Phosphinooxazoline (PHOX) ligands **(*S*)-L1**, **(*S*)-L2**, and achiral GlyPhox were prepared by methods described in our previous work.[3] Di-benzoylated allylic alkylation substrate **3g** was prepared according to the method of Korch.[4] Tris(4,4'-methoxydibenzylideneacetone)dipalladium(0) [$Pd_2(pmdba)_3$] was prepared according to the method of Ibers[5] or Fairlamb.[6] AgOPiv was prepared using Grubbs' procedure.[7] *tert*-Butyl ((phenylsulfonyl)methyl)carbamate and benzyl ((phenylsulfonyl)methyl)carbamate were prepared according to the method of Zwierzak or Dikshit.[8] Benzyl 3-oxopiperazine-1-carboxylate was prepared according to the method of Batey.[9] 2-chloroallyl chloroformate was prepared according to the method of Stoltz.[10]

Experimental Procedures for the Synthesis of Piperazinone Allylic Alkylation Substrates

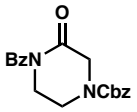


tert-butyl 4-benzoyl-3-oxopiperazine-1-carboxylate (SI-1). To a solution of *tert*-butyl 3-oxopiperazine-1-carboxylate **1** (5.0 g, 24.9 mmol, 1 equiv) in THF (250 mL) at −78 °C was added dropwise *n*BuLi (11.4 mL, 2.4M solution in hexane, 27.5 mmol, 1.1 equiv) over 20 minutes. The resulting yellow solution was stirred for 10 min at −78 °C. Benzoyl chloride (3.48 mL, 30.0 mmol, 1.2 equiv) was then added dropwise at −78 °C, giving an orange solution. The reaction was stirred for 2.5 h at −78 °C, quenched by addition of saturated aqueous NH_4Cl (100 mL), and diluted with ethyl acetate (100 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, decanted, and concentrated under reduced pressure onto silica gel. The silica-loaded crude reaction mixture was purified by silica gel flash column chromatography (10% →15% →20% EtOAc/hexanes) to give protected ketopiperazine **SI-1** as a white solid (3.2 g, 42.1% yield). Product identity was confirmed by comparison to previously reported characterization data.[11]

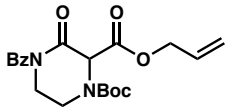


tert-butyl 4-(4-methoxybenzoyl)-3-oxopiperazine-1-carboxylate (SI-2). To a solution of *tert*-Butyl 3-oxopiperazine-1-carboxylate (5.0 g, 24.9 mmol, 1 equiv) in THF (250 mL) at −78 °C was added dropwise *n*BuLi (11.4 mL, 2.4M solution in hexane, 27.5 mmol, 1.1 equiv) over 20 minutes. The resulting yellow solution was stirred for 10 min at −78 °C. Anisoyl chloride (4.1 mL, 30.0 mmol, 1.2 equiv) was then added dropwise at −78 °C, giving a bright orange solution. The reaction was stirred for 2 h at −78 °C, quenched by addition of saturated aqueous NH_4Cl (100 mL), and diluted with ethyl acetate (100 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, decanted, and

concentrated under reduced pressure onto silica gel. The silica-loaded crude reaction mixture was filtered through a plug of silica (1% →2% MeOH/CH_2Cl_2) to give crude anisoyl protected ketopiperazine **SI-2** as a white foam, which was directly used without further purification in subsequent acylation reactions with allyl cyanoformate.

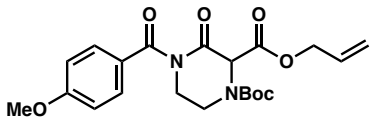


benzyl 4-benzoyl-3-oxopiperazine-1-carboxylate (SI-3). To a solution of benzyl 3-oxopiperazine-1-carboxylate[9] (1.0 g, 4.3 mmol, 1.0 equiv) in THF (42 mL) at −78 °C was added dropwise *n*BuLi (1.96 mL, 2.4M solution in hexane, 4.7 mmol, 1.1 equiv) over 20 minutes. The solution was stirred for 10 min at −78 °C. Benzoyl chloride (0.595 mL, 5.1 mmol, 1.2 equiv) was then added dropwise at −78 °C, giving a light yellow solution. The reaction was stirred for 1 h at −78 °C, quenched by addition of saturated aqueous NH_4Cl (50 mL), and diluted with ethyl acetate (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, decanted, and concentrated under reduced pressure onto silica gel. The silica-loaded crude reaction mixture was purified by silica gel flash column chromatography (33% EtOAc/hexanes) to give Bz-Cbz-protected ketopiperazine **SI-3** as a white solid (1.0 g, 70.0% yield); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.61 – 7.56 (m, 2H), 7.54 – 7.49 (m, 1H), 7.44 – 7.31 (m, 7H), 5.21 (s, 2H), 4.30 (s, 2H), 3.95 (dd, *J* = 6.8, 4.4 Hz, 2H), 3.83 (dd, *J* = 6.9, 4.3 Hz, 2H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 172.8, 168.0, 167.6, 154.5, 136.0, 135.0, 132.3, 128.7, 128.5, 128.4, 128.3, 128.3, 68.0, 48.5, 43.3, 41.7, 41.4; **IR (Neat Film, NaCl)** 3386, 3063, 3033, 2954, 2894, 1706, 1600, 1584, 1498, 1449, 1422, 1394, 1367, 1302, 1231, 1177, 1162, 1123, 1060, 1028, 1010, 944, 857, 796, 765, 731, 699, 639, 612 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_{19}H_{19}N_2O_4$ $[M+H]^+$: 339.1339, found 339.1338.

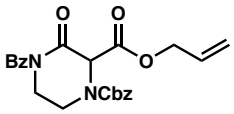


2-allyl 1-(tert-butyl) 4-benzoyl-3-oxopiperazine-1,2-dicarboxylate (2). To a solution of Bz-protected oxopiperazine **SI-1** (1.5 g, 4.9 mmol, 1.0 equiv) in THF (40 mL) at −78 °C was added LiHMDS (907 mg, 5.42 mmol, 1.10 equiv.) in THF (10mL) dropwise. The resulting orange reaction mixture was stirred for 15 min at −78 °C. Then, allyl cyanoformate (590 µL, 5.2 mmol, 1.05 equiv) was added dropwise at −78 °C, giving a yellow solution. After stirring for 1.5 h at −78 °C, the reaction was quenched with saturated aqueous NH_4Cl (20 mL) and diluted with ethyl acetate (50 mL). The aqueous phase was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, decanted, and concentrated under reduced pressure onto silica. The silica-loaded crude mixture was purified by silica gel flash chromatography (10% → 20% EtOAc/hexanes) to give the allyl ester **2** as a white solid (1.3 g, 68% yield): **^{1}H NMR (500 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 7.59 (d, *J* = 7.7 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 5.92 (m, 1H), 5.44 – 5.07 (m, 3H), 4.84 – 4.57 (m, 2H), 4.28

– 3.61 (m, 4H), 1.43 (br s, 9H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 172.7, 166.9, 164.4, 154.1, 153.5, 134.6, 132.6, 131.0, 128.6, 128.4, 119.9, 119.4, 82.2, 82.0, z67.1, 62.7, 61.7, 43.2, 42.6, 41.5, 40.2, 29.4, 28.3; **IR (Neat Film, NaCl)** 2978 1746 1695 1600 1450 1393 1367 1310 1277 1231 1177 1158 1127 1088 1059 1009 958 861 794 770 728 694 623 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_{16}H_{17}N_2O_6$ [(M-*t*Bu)+H]$^+$: 333.1081, found 333.1075.

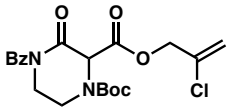


2-allyl 1-(tert-butyl) 4-(4-methoxybenzoyl)-3-oxopiperazine-1,2-dicarboxylate (3b). Following the procedure described for the preparation of **2**, anisoyl protected oxopiperazine **SI-2** (1.0 g, 3.0 mmol, 1.0 equiv) was treated with LiHMDS (550 mg, 3.3 mmol, 1.1 equiv) and acylated with allyl cyanoformate (336 μL, 3.1 mmol, 1.05 equiv) to give, after purification by silica gel flash chromatography (Dry load SiO_2, 18% EtOAc/hexanes), allyl ester **3b** as a white solid (566 mg, 45% yield): **^{1}H NMR (400 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 7.61 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.91 (ddt, *J* = 16.4, 10.8, 5.8 Hz, 1H), 5.46–5.12 (m, 3H), 4.70 (s, 2H), 4.13–3.65 (m, 4H), 3.81 (s, 3H), 1.46 (m, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 171.9, 171.8, 167.0, 164.4, 164.2, 163.4, 154.0, 153.4, 131.4, 131.0, 126.3, 119.6, 119.2, 113.6, 82.0, 81.8, 66.9, 62.5, 61.6, 55.5, 43.3, 42.8, 41.5, 40.1, 28.2; **IR (Neat Film, NaCl)** 3384, 3060, 2978, 2843, 2568, 2049, 1732, 1605, 1580, 1513, 1456, 1372, 1258, 1088, 1059, 959, 844, 769, 736, 706, 634 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_{21}H_{27}N_2O_7$ [M+H]$^+$: 419.1813, found 419.1815.

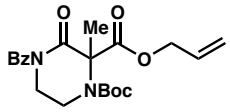


2-allyl 1-benzyl 4-benzoyl-3-oxopiperazine-1,2-dicarboxylate (3c). Following the procedure described for the preparation of **2**, Cbz protected oxopiperazine **SI-3** (1.0 g, 3.0 mmol, 1.0 equiv) was treated with LiHMDS (544 mg, 3.3 mmol, 1.1 equiv) and acylated with allyl cyanoformate (331 μL, 3.1 mmol, 1.05 equiv) to give, after purification by silica gel flash chromatography (dry load SiO_2, 20 → 25% EtOAc/hexanes), allyl ester **3a** as a white solid (720 mg, 58% yield): **^{1}H NMR (500 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 7.65 – 7.56 (m, 2H), 7.56 – 7.46 (m, 1H), 7.46 – 7.28 (m, 7H), 5.87 (dtd, *J* = 47.5, 10.7, 5.4 Hz, 1H), 5.55 – 5.04 (m, 5H), 4.84 – 4.48 (m, 2H), 4.24 – 3.99 (m, 2H), 3.99 – 3.66 (m, 2H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 172.4, 172.3, 166.5, 164.0, 163.8, 154.8, 154.2, 135.7, 135.6, 134.4, 132.5, 130.9, 130.8, 128.7, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 128.1, 119.6, 119.5, 68.3, 68.2, 67.2, 67.1, 62.1, 61.9, 42.8, 42.3, 41.3, 40.8; **IR (Neat Film, NaCl)** 3386, 3064, 3033, 2955, 2897, 1746, 1713, 1694, 1651, 1600, 1584, 1498, 1450, 1417, 1368, 1304, 1278, 1229, 1195, 1178,

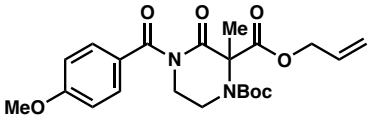
1160, 1124, 1088, 1061, 1014, 985, 951, 860, 794, 768, 729, 696, 675, 623 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calc'd for $C_{23}H_{23}N_2O_6$ $[M+H]^+$: 423.1551, found 423.1547.



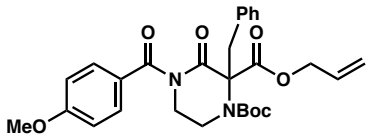
1-(tert-butyl) 2-(2-chloroallyl) 4-benzoyl-3-oxopiperazine-1,2-dicarboxylate (3d). Following the procedure described for the preparation of **2**, benzoyl protected oxopiperazine **SI-1** (440 mg, 1.5 mmol, 1.0 equiv) was treated with LiHMDS (267 mg, 1.6 mmol, 1.1 equiv) and acylated with 2-chloroallyl chloroformate[10] (235 mg, 1.5 mmol, 1.05 equiv) to give, after purification by silica gel flash chromatography (Dry load SiO_2, 15% EtOAc/hexanes), 2-chloroallyl ester **3d** as an off-white solid (431 mg, 70% yield): **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (a mixture of two rotamers) 7.59–7.54 (m, 2H), 7.50–7.44 (m, 1H), 7.43–7.37 (m, 2H), 6.67 (m, 1H), 5.42–5.33 (m, 2H), 4.54 (m, 2H), 3.95–3.89 (m, 2H), 3.72 (t, J = 5.2 Hz, 2H), 1.51 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ (a mixture of two rotamers) 167.5, 167.3, 152.4, 152.2, 151.1, 151.0, 135.1, 134.9, 134.3, 131.3, 131.2, 128.5, 128.4, 128.0, 127.9, 126.7, 115.9, 115.7, 107.9, 107.6, 82.3, 82.2, 69.9, 69.8, 44.2, 43.1, 42.3, 41.7, 28.3; **IR (Neat Film, NaCl)** 3396, 3129, 3062, 2979, 2936, 2253, 1770, 1691, 1372, 1242, 1050, 987, 950, 922, 859, 839, 764, 731, 707, 647 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calculated for $C_{20}H_{24}ClN_2O_6$ $[M+H]^+$: 423.1317, found 423.1316.



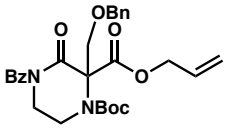
2-allyl 1-(tert-butyl) 4-(4-methoxybenzoyl)-2-methyl-3-oxopiperazine-1,2-dicarboxylate (3e). Sodium hydride (60% in mineral oil, 25 mg, 0.62 mmol, 1.2 equiv) was added to a solution of allyl ester **2** (200 mg, 0.52 mmol, 1.0 equiv) in THF (5 mL) at 0 °C. After stirring for 30 min at 0 °C, MeI (160 μL, 2.57 mmol, 5.0 equiv) was added. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction was quenched with aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over anhydrous Na_2SO_4, decanted, and concentrated under reduced pressure onto silica gel. The silica-loaded residue was purified by silica gel flash chromatography (20% EtOAc/hexanes) to give methylated allyl ester **3e** as a colorless oil (180 mg, 85% yield): **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.59 – 7.46 (m, 3H), 7.46 – 7.32 (m, 2H), 5.92 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.41 – 5.19 (m, 2H), 4.66 (d, *J* = 5.8 Hz, 2H), 4.24 – 4.09 (m, 1H), 4.05 – 3.90 (m, 2H), 3.81 – 3.64 (m, 1H), 1.84 (s, 3H), 1.46 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ (a mixture of two rotamers) 172.5, 169.2, 168.0, 153.2, 134.8, 132.4, 131.5, 128.4, 128.0, 119.1, 82.7, 68.7, 66.9, 43.7, 40.9, 28.3, 21.5; **IR (Neat Film, NaCl)** 3384, 3064, 2980, 2939, 2876, 1962, 1766, 1694, 1600, 1584, 1451, 1394, 1368, 1306, 1270, 1232, 1206, 1164, 1096, 1060, 1032, 1016, 993, 968, 936, 854, 795, 770, 727, 696, 675, 633, 618 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calculated for $C_{16}H_{19}N_2O_4$ $[(M-Boc)+H]^+$: 303.1341, found 303.1339.



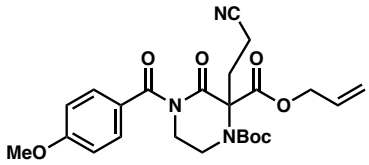
2-allyl 1-(tert-butyl) 4-(4-methoxybenzoyl)-2-methyl-3-oxopiperazine-1,2-dicarboxylate (3f). Following the procedure described for the preparation of **3e**, anisoyl protected oxopiperazine **3b** (120 mg, 0.29 mmol, 1.0 equiv) was treated with NaH (60% in mineral oil, 13 mg, 0.32 mmol, 1.1 equiv) and methylated with MeI (90 μL, 1.43 mmol, 5.0 equiv) to give, after purification by silica gel flash chromatography (dry load SiO_2, 15% → 20% → 25% → 30% EtOAc/hexanes), methylated allyl ester **3f** as a colorless oil (110 mg, 89% yield): **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.56 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.9 Hz, 2H), 5.92 (ddt, J = 17.2, 10.4, 5.8 Hz, 1H), 5.40 – 5.17 (m, 2H), 4.66 (d, J = 5.8 Hz, 2H), 4.15 – 4.02 (m, 1H), 4.02 – 3.87 (m, 2H), 3.83 (s, 3H), 3.80 – 3.67 (m, 1H), 1.84 (s, 3H), 1.46 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.8, 169.0, 168.1, 163.4, 153.2, 131.5, 131.0, 126.6, 119.0, 113.7, 82.6, 68.5, 66.8, 55.5, 43.8, 41.0, 28.3, 21.6; **IR (Neat Film, NaCl)** 3081, 2978, 2938, 2842, 1766, 1702, 1604, 1579, 1512, 1460, 1394, 1368, 1308, 1287, 1259, 1235, 1208, 1169, 1114, 1095, 1060, 1021, 1004, 969, 933, 845, 789, 770, 733, 706, 648, 634 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calculated for $C_{18}H_{21}N_2O_7$ $[(M-tBu)+H]^+$: 377.1343, found 377.1339.



2-allyl 1-(tert-butyl) 2-benzyl-4-(4-methoxybenzoyl)-3-oxopiperazine-1,2-dicarboxylate (3h). Following the procedure described for the preparation of **3e**, anisoyl-protected allyl ester **3b** (200 mg, 0.48 mmol, 1.0 equiv) was treated with potassium hydride (23 mg, 0.57 mmol, 1.2 equiv) and alkylated with benzyl bromide (170 μL, 1.43 mmol, 3.0 equiv) to give, after purification by silica gel flash chromatography (Dry load SiO_2, 20% → 25% EtOAc/hexanes), the benzyl ester **3h** as a colorless oil (100 mg, 41% yield) (Note: attempts using sodium hydride as a base failed to give conversion of starting material. Instead, potassium hydride resulted in conversion to the desired product.): **^{1}H NMR (400 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 7.52 (m, 2H), 7.42 – 7.23 (m, 3H), 7.11 (m, 2H), 6.92 – 6.75 (m, 2H), 5.97 (ddt, J = 17.2, 10.4, 5.8 Hz, 1H), 5.50 – 5.17 (m, 2H), 4.87 – 4.57 (m, 2H), 3.86 (s, 3H), 3.79 – 3.56 (m, 4H), 2.95 (ddd, J = 13.3, 7.4, 3.0 Hz, 1H), 2.86 (br s, 1H), 1.55 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 172.1, 168.0, 167.4, 166.9, 163.4, 153.6, 153.4, 136.0, 135.3, 131.8, 131.3, 130.7, 128.8, 128.7, 128.4, 128.2, 127.8, 127.7, 127.5, 126.6, 119.4, 118.9, 113.7, 82.9, 81.8, 72.7, 67.0, 66.5, 55.6, 44.5, 43.0, 42.2, 41.4, 40.8, 40.0, 38.8, 28.5; **IR (Neat Film, NaCl)** 2978, 1764, 1698, 1604, 1512, 1496, 1455, 1394, 1366, 1307, 1282, 1256, 1196, 1155, 1078, 1020, 1000, 921, 844, 768 733, 704 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calculated for $C_{28}H_{33}N_2O_7$ $[M+H]^+$: 509.2282, found 509.2285.

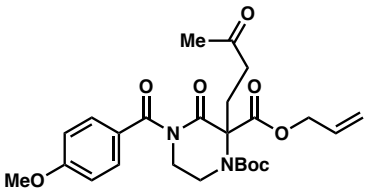


2-allyl 1-(tert-butyl) 4-benzoyl-2-((benzyloxy)methyl)-3-oxopiperazine-1,2-dicarboxylate (3i). Following the procedure described for the preparation of **3e**, allyl ester **2** (150 mg, 0.39 mmol, 1.00 equiv) was treated with sodium hydride (17 mg, 0.42 mmol, 1.1 equiv) and alkylated with benzyl chloromethyl ether (107 μL, 0.77 mmol, 2.0 equiv) to give, after purification by silica gel flash chromatography (Dry load SiO_2, 10% → 15% EtOAc/hexanes), benzyloxy methyl ether **3i** as a colorless oil (50 mg, 55% yield BRSM): **^{1}H NMR (500 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 7.64 – 7.55 (m, 2H), 7.51 – 7.44 (m, 1H), 7.41 – 7.27 (m, 7H), 5.88 (ddt, *J* = 17.3, 10.4, 5.8 Hz, 1H), 5.40 – 5.17 (m, 2H), 4.74 – 4.47 (m, 4H), 4.38 (m, 1H), 4.17 (m, 1H), 4.08 – 3.84 (m, 4H), 1.42 (m, 9H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 173.0, 167.4, 167.2, 166.5, 153.6, 153.1, 141.0, 137.9, 137.5, 134.8, 132.4, 131.6, 131.1, 128.7, 128.7, 128.6, 128.4, 128.3, 128.0, 127.7, 127.6, 127.1, 119.5, 118.9, 82.7, 81.9, 73.9, 73.3, 72.6, 71.2, 71.1, 66.8, 65.4, 43.6, 43.4, 42.5, 41.7, 28.4, 28.3; **IR (Neat Film, NaCl)** 3528, 3064, 3031, 2978, 2934, 1762, 1694, 1600, 1496, 1453, 1394, 1366, 1314, 1270, 1231, 1205, 1161, 1094, 1055, 1014, 972, 941, 854, 795, 770, 730, 696, 674, 624 cm^{-1}; **HRMS (MM: ESI-APCI)** *m/z* calculated for $C_{24}H_{25}N_2O_7$ $[(M-t\text{Bu})+H]^+$: 453.1656, found 453.1649.

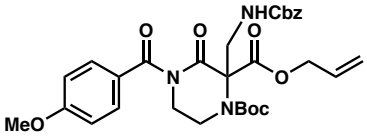


2-allyl 1-(tert-butyl) 2-(2-cyanoethyl)-4-(4-methoxybenzoyl)-3-oxopiperazine-1,2-dicarboxylate (3j). DBU (7.1 μL, 0.048 mmol, 0.10 equiv) was added to a solution of allyl ester **3b** (200 mg, 0.478 mmol, 1.0 equiv) and acrylonitrile (94 μL, 1.43 mmol, 3.0 equiv) in DMF (2.4 mL) at room temperature. After stirring for 2 h at 70 °C and 24 h at 55 °C, additional DBU (14 μL, 0.1 mmol, 0.2 equiv) was added and the orange solution was maintained at 70 °C for 4 h. Then, additional DBU (21 μL, 0.143 mmol, 0.30 equiv) was added and the mixture was stirred at 70 °C for 3 h. After allowing the reaction mixture to cool to room temperature, the reaction was quenched with saturated aqueous NH_4Cl (2 mL) and diluted with EtOAc (6 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, decanted, and concentrated under reduced pressure onto silica gel. The silica-loaded residue was purified by flash chromatography (20% EtOAc/hexanes) to give the *α*-cyanoethylated allyl ester **3j** as a pale yellow oil (77.6 mg, 34% yield): **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.54 (s, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 5.92 (ddt, *J* = 17.2, 10.4 Hz, 5.9 Hz, 1H), 5.36 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.29 (d, J = 10.5 Hz, 1H), 4.69 (d, *J* = 5.8 Hz, 2H), 4.25 (s, 1H), 4.06 (ddd, *J* = 13.1, 5.7, 3.1 Hz, 1H), 3.96 (ddd, *J* = 13.1, 8.6, 3.4 Hz, 1H), 3.83 (s, 3H), 3.64 – 3.49 (m,

1H), 2.77 (s, 2H), 2.49 (m, 1H), 2.44 – 2.31 (m, 1H), 1.47 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.7, 167.24, 166.3, 163.5, 153.4, 131.1, 126.2, 119.6, 119.1, 113.8, 82.9, 70.5, 67.3, 55.5, 43.9, 42.3, 29.8, 28.2, 12.8; **IR (Neat Film, NaCl)** 2978, 2249, 1760, 1694, 1604, 1579, 1512, 1462, 1394, 1368, 1311, 1258, 1160, 1018, 933, 846, 769, 737, 704 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{24}H_{30}N_3O_7$ $[M+H]^+$: 472.2078, found 472.2078.

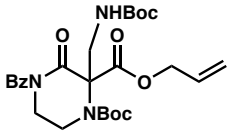


2-allyl 1-(tert-butyl) 4-(4-methoxybenzoyl)-3-oxo-2-(3-oxobutyl)piperazine-1,2-dicarboxylate (3k). To a solution of allyl ester **3b** (200 mg, 0.5 mmol, 1.0 equiv) and methyl vinyl ketone (80 µL, 0.96 mmol, 2.0 equiv) in acetone (2 mL) at room temperature was added DBU (7.1 µL, 0.05 mmol, 0.1 equiv). After stirring for 24 h at 55 °C, additional DBU (7.1 µL, 0.05 mmol, 0.1 equiv) was added and the orange solution was maintained at 55 °C for an additional 24 h. The reaction mixture was allowed to cool to ambient temperature and concentrated under reduced pressure onto silica gel. The silica-loaded crude reaction mixture was purified by silica gel flash column chromatography (33% EtOAc/hexanes) to afford the ketone **3k** as a pale yellow oil (90 mg, 39% yield): **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.56 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 5.92 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.35 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.26 (d, *J* = 10.4 Hz, 1H), 4.71 – 4.60 (m, 2H), 4.11 – 3.93 (m, 3H), 3.82 (s, 3H), 3.71 – 3.59 (m, 1H), 2.72 (q, *J* = 9.3, 8.1 Hz, 1H), 2.60 (dt, *J* = 9.6, 6.2 Hz, 3H), 2.10 (s, 3H), 1.45 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 207.8, 172.0, 167.9, 167.4, 163.4, 153.5, 131.5, 131.1, 126.6, 119.2, 113.7, 82.4, 70.6, 66.9, 55.5, 43.5, 42.1, 38.8, 29.8, 28.7, 28.3; **IR (Neat Film, NaCl):** 2977, 2934, 1761, 1704, 1604, 1512, 1456, 1394, 1367, 1312, 1257, 1199, 1168, 1090, 1018, 845, 768 cm^{-1}; **HRMS (MM: ESI-APCI)**: *m/z* calc'd for $C_{25}H_{33}N_2O_8$ $[M+H]^+$: 489.2231, found: 489.2228.



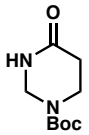
2-allyl 1-(tert-butyl) 2-((((benzyloxy)carbonyl)amino)methyl)-4-(4-methoxybenzoyl)-3-oxopiperazine-1,2-dicarboxylate (3l). Following the procedure described for the preparation of **3m**, anisoyl-protected allyl ester **3b** (400 mg, 0.96 mmol, 1.0 equiv) was treated with Cs_2CO_3 (779 mg, 02.39 mmol, 2.5 equiv) and alkylated with benzyl ((phenylsulfonyl)methyl)carbamate[8] (350 mg, 1.15 mmol, 2.5 equiv) to give, after purification by silica gel flash chromatography (Dry load SiO_2, 10% → 15% → 20% EtOAc/hexanes), the aminomethyl allyl ester **3l** as a white foam (300 mg, 54% yield): **^{1}H NMR (400 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 7.69 – 7.50 (m, 2H), 7.41 – 7.25

(m, 5H), 6.95 – 6.72 (m, 2H), 5.92 (ddt, *J* = 17.3, 10.4, 5.9 Hz, 1H), 5.49 – 4.96 (m, 5H), 4.85 – 4.53 (m, 2H), 4.27 – 3.87 (m, 5H), 3.83 (d, *J* = 14.6 Hz, 3H), 3.60 (d, *J* = 22.7 Hz, 1H), 1.47 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 171.7, 167.3, 166.5, 163.4, 156.8, 153.7, 152.7, 136.4, 134.21, 132.5, 131.5, 131.2, 129.4, 129.3, 128.9, 128.6, 128.3, 126.5, 119.8, 119.3, 113.7, 83.1, 82.1, 71.4, 70.6, 68.3, 67.8, 67.0, 55.5, 45.0, 44.2, 43.7, 42.9, 41.9, 28.3; **IR (Neat Film, NaCl)** 3366, 2977, 1704, 1604, 1513, 1456, 1394, 1367, 1313, 1257, 1232, 1169, 1091, 1018, 1002, 845, 767, 698 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{30}H_{36}N_3O_9$ $[M+H]^+$: 582.2446, found 582.2438.



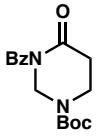
2-allyl 1-(tert-butyl) 4-benzoyl-2-(((tert-butoxycarbonyl)amino)methyl)-3-oxopiperazine-1,2-dicarboxylate (3m). To a suspension of allyl ester **2** (200 mg, 0.5 mmol, 1.0 equiv) and *tert*-butyl ((phenylsulfonyl)methyl)carbamate[8] (168 mg, 0.6 mmol, 1.2 equiv), in dichloromethane (2.5 mL) at room temperature was added Cs_2CO_3 (419 mg, 1.3 mmol, 2.5 equiv). After stirring for 3 h, saturated aqueous NH_4Cl (1 mL) was added and the biphasic mixture was vigorously stirred for 20 min. The aqueous phase was extracted with dichloromethane (3 x 3 mL). The combined organic phases were dried over anhydrous Na_2SO_4, decanted, and concentrated under reduced pressure onto silica gel. The silica-loaded crude reaction mixture was purified by silica gel flash column chromatography (15% EtOAc/hexanes) to give methylcarbamate allyl ester **3m** as a white foam (202 mg, 76% yield): **^{1}H NMR (400 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 7.55 (d, *J* = 7.5 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 2H), 5.91 (ddt, *J* = 16.5, 10.4, 5.8 Hz, 1H), 5.34 – 5.27 (m, 2H), 4.96 (m, 1H), 4.66 (br s, 2H), 4.19 – 3.85 (m, 5H), 3.79 – 3.64 (m, 1H), 1.48 (s, 9H), 1.40 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 172.4, 167.3, 166.8, 156.1, 153.6, 152.9, 134.9, 132.4, 131.7, 131.1, 128.3, 128.3, 119.6, 119.0, 83.1, 82.1, 79.9, 71.4, 70.6, 67.0, 44.3, 43.8, 43.2, 42.2, 41.6, 28.4, 28.3; **IR (Neat Film, NaCl)** 3386, 2978, 1760, 1698, 1601, 1505, 1451, 1394, 1367, 1314, 1232, 1203, 1164, 1092, 1067, 1012, 915, 854, 766, 730, 696 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{26}H_{36}N_3O_8$ $[M+H]^+$: 518.2497, found 518.2496.

Experimental Procedures for the Synthesis of Tetrahydropyrimidinone Allylic Alkylation Substrates

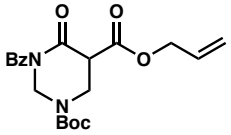


***tert*-Butyl 4-oxotetrahydropyrimidine-1(2*H*)-carboxylate (SI-4)**. A solution of 3-aminopropanamide hydrochloride (5 g, 40.1 mmol, 1.0 equiv), potassium hydroxide (3.38

g, 60.2 mmol, 1.5 equiv), and formaldehyde (37% in water, 5.97 mL, 80.3 mmol, 2.0 equiv) in ethanol (13 mL) was stirred at reflux for 4 h. The suspension was then maintained at 55 °C while triethylamine (5.5 mL, 40.1 mmol, 1 equiv) and di-*tert*-butyl dicarbonate (9.2 g, 42.1 mmol, 1.05 equiv) were added successively. The reaction was stirred for 2 h at 55 °C and then allowed to cool to ambient temperature. The precipitate was filtered off, the filtrate was concentrated under reduced pressure, and was then purified by silica gel flash chromatography (1 → 3% $MeOH/CH_2Cl_2$) to afford Boc-protected tetrahydropyrimidinone **SI-4** as a white solid (4.09 g, 51% yield over two steps): **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.14 – 7.60 (m, 1H), 4.77 – 4.61 (m, 2H), 3.58 (t, *J* = 6.5 Hz, 2H), 2.41 (t, *J* = 6.5 Hz, 2H), 1.41 (s, 9H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 171.5, 153.8, 153.4, 81.1, 54.8, 54.0, 40.4, 39.4, 31.4, 28.3; **IR (Neat Film, NaCl)** 3193, 2970, 1710, 1643, 1488, 1404, 1366, 1326, 1276, 1245, 1210, 1159, 1136, 1020, 949, 776 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_9H_{17}N_2O_3$ $[M+H]^+$: 201.1234, found 201.1231.

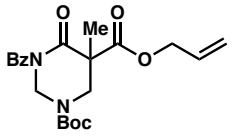


***tert*-Butyl 3-benzoyl-4-oxotetrahydropyrimidine-1(2*H*)-carboxylate (SI-5).** To a solution of tetrahydropyrimidinone **SI-4** (2.07 g, 10.4 mmol, 1.0 equiv) in THF (100 mL) at −78 °C was added *n*-butyllithium (2.2 M in hexanes, 4.94 mL, 10.9 mmol, 1.05 equiv) dropwise over 10 min. After stirring the solution at −78 °C for 20 min, benzoyl chloride (1.43 mL, 12.4 mmol, 1.2 equiv) was added dropwise at −78 °C. The reaction solution was stirred at −78 °C for 40 min, allowed to warm up to room temperature, and was then quenched with saturated aqueous NH_4Cl (50 mL). The mixture was diluted with EtOAc (100 mL) and the aqueous phase was extracted with EtOAc (3 x 80 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure onto silica gel. The silica-loaded residue was purified by silica gel flash chromatography (30% EtOAc/hexanes) to give Bz-protected tetrahydropyrimidinone **SI-5** as a white solid (2.72 g, 86% yield): **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.55 (dt, *J* = 8.3, 1.4 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 5.28 (s, 2H), 3.74 (t, *J* = 6.6 Hz, 2H), 2.68 (t, *J* = 6.6 Hz, 2H), 1.49 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.3, 170.7, 153.8, 135.0, 132.2, 128.4, 128.2, 81.7, 57.0, 40.4, 33.4, 28.3; **IR (Neat Film, NaCl)** 2978, 1698, 1480, 1450, 1408, 1367, 1304, 1266, 1239, 1141, 1015, 936, 863, 797, 700, 618 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{16}H_{21}N_2O_4$ $[M+H]^+$: 305.1496, found 305.1500.



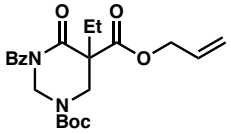
5-Allyl 1-(*tert*-butyl) 3-benzoyl-4-oxotetrahydropyrimidine-1,5(2*H*)-dicarboxylate

(SI-6). To a solution of diisopropylamine (224 μL, 1.59 mmol, 1.2 equiv) in THF (3 mL) at −78 °C was added *n*-butyllithium (2.2 M in hexanes, 664 μL, 1.46 mmol, 1.1 equiv). The solution was maintained at −78 °C for 15 min and then cannulated over 10 min into a solution of Bz-protected tetrahydropyrimidine **SI-5** (404 mg, 1.33 mmol, 1.0 equiv) in THF (10 mL) at −78 °C. After stirring the solution at −78 °C for 25 min, allyl cyanoformate (156 μL, 1.46 mmol, 1.1 equiv) was added dropwise at −78 °C. The reaction mixture was maintained at −78 °C for 50 min and was then quenched with saturated aqueous NH_4Cl (10 mL). The reaction mixture was diluted with EtOAc (10mL) and allowed to warm to room temperature. The aqueous phase was extracted with EtOAc (3 x 15 mL) and the combined organic phases were dried over anhydrous Na_2SO_4, decanted, and concentrated under reduced pressure onto silica gel. The silica-loaded residue was purified by silica gel flash chromatography (18 → 20 → 30% EtOAc/hexanes) to give re-isolated starting material **SI-5** (154 mg, 38% yield) and allyl ester **SI-6** as a white crystalline solid (310 mg, 60% yield, 97% yield based on recovered starting material): **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.70 (d, *J* = 7.2 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 5.95 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.37 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.36 (m, 1H), 5.30 (dd, *J* = 10.4, 1.3 Hz, 1H), 5.17 (d, *J* = 12.6 Hz, 1H), 4.69 (d, *J* = 6.0 Hz, 2H), 4.27 (ddd, *J* = 13.7, 5.4, 1.2 Hz, 1H), 3.85 (dd, *J* = 13.7, 6.2 Hz, 1H), 3.63 (t, *J* = 5.7 Hz, 1H), 1.49 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.9, 167.8, 167.0, 153.4, 134.6, 132.5, 131.3, 128.7, 128.3, 119.7, 82.3, 67.0, 58.5, 50.1, 43.9, 28.3; **IR (Neat Film, NaCl)** 3406, 3064, 2978, 2935, 1714, 1601, 1480, 1450, 1416, 1369, 1287, 1148, 1072, 1017, 934 , 859, 796, 768, 736, 703, 626 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{20}H_{25}N_2O_6$ $[M+H]^+$: 389.1707, found 389.1708.

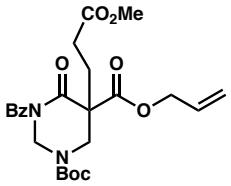


1-(*tert*-butyl) 3-benzoyl-5-methyl-4-oxotetrahydropyrimidine-1,5(2*H*)-dicarboxylate (5a). To a solution of allyl ester **SI-6** (100 mg, 0.26 mmol, 1.0 equiv) in acetonitrile (2.6 mL) at 0 °C was added cesium carbonate (168 mg, 0.52 mmol, 2.0 equiv). After stirring the suspension for 30 min at 0 °C, methyl iodide (48 μL, 0.77 mmol, 3.0 equiv) was added. The reaction mixture was stirred for 3 h at 0 °C and diluted with saturated aqueous NH_4Cl (2 mL) and EtOAc (2 mL). The aqueous phase was extracted with EtOAc (4 x 3 mL) and the combined organic phases were dried over anhydrous Na_2SO_4, decanted, and concentrated under reduced pressure onto silica gel. The residue was purified by silica gel flash chromatography (15% EtOAc/hexanes) to give methylated allyl ester **5a** as a colorless oil (100 mg, 95% yield): **^{1}H NMR (500 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 7.71 (d, *J* = 15.3 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 6.8 Hz, 2H), 5.96 (ddt, *J* = 16.6, 10.4, 6.0 Hz, 1H), 5.48 – 5.17 (m, 4H), 4.71 (d, *J* = 6.1 Hz, 2H), 4.43 (m, 1H), 3.38 (m, 1H), 1.49 (s, 9H), 1.47 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 173.2, 170.9, 170.7, 153.2, 135.0, 132.3, 131.3, 128.4, 128.2, 119.7, 82.1, 67.1, 58.9, 58.1, 52.8, 50.6, 50.3, 28.3, 19.3; **IR (Neat Film, NaCl)** 3406, 3065, 2980, 2939, 1714, 1602, 1450, 1423, 1369, 1288, 1251, 1162, 1134, 1104, 1028, 984, 938, 902, 857, 804, 765, 732,

697, 657, 635 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{21}H_{27}N_2O_6$ $[M+H]^+$: 403.1864, found 403.1868.

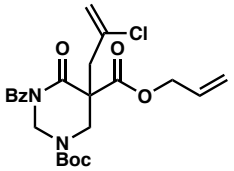


5-allyl 1-(tert-butyl) 3-benzoyl-5-ethyl-4-oxotetrahydropyrimidine-1,5(2H)-dicarboxylate (5b). Following the procedure described for the preparation of **5a**, allyl ester **SI-6** (200 mg, 0.52 mmol, 1.0 equiv) was treated with cesium carbonate (336 mg, 1.03 mmol, 2.0 equiv) and alkylated with ethyl iodide (124 μL, 1.54 mmol, 3.0 equiv) to give, after purification by silica gel flash chromatography (dry load SiO_2, 15% EtOAc/hexanes), ethylated allyl ester **5b** as a colorless oil (182 mg, 85% yield): **^{1}H NMR (400 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 7.70 (d, *J* = 8.0 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 2H), 5.95 (ddt, *J* = 16.6, 10.4, 6.0 Hz, 1H), 5.38 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.31 (d, *J* = 10.3 Hz, 2H), 5.20 (d, *J* = 12.5 Hz, 1H), 4.70 (t, *J* = 5.5 Hz, 2H), 4.47 – 4.26 (m, 1H), 3.49 (d, *J* = 13.5 Hz, 1H), 1.96 (q, *J* = 7.5 Hz, 2H), 1.49 (s, 9H), 0.96 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 172.9, 170.4, 170.1, 169.8, 153.2, 135.0, 132.3, 131.2, 128.4, 128.2, 119.8, 81.9, 66.9, 57.9, 57.4, 56.7, 47.8, 47.4, 28.3, 26.4, 9.1; **IR (Neat Film, NaCl)** 2976, 1703, 1450, 1422, 1367, 1288, 1247, 1156, 1134, 1015, 942, 894, 802, 766, 718, 696 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{22}H_{29}N_2O_6$ $[M+H]^+$: 417.2020, found 417.2019.

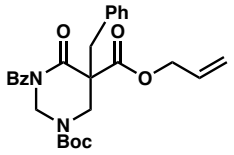


5-allyl 1-(tert-butyl) 3-benzoyl-5-(3-methoxy-3-oxopropyl)-4-oxotetrahydropyrimidine-1,5(2H)-dicarboxylate (5c). To a suspension of allyl ester **SI-6** (100 mg, 0.26 mmol, 1.0 equiv) and potassium carbonate (178 mg, 1.29 mmol, 5.0 equiv) in acetone (1.0 mL) at room temperature was added methyl acrylate (47 μL, 0.52 mmol, 2.0 equiv). The reaction mixture was stirred for 3.5 h at 55 °C, allowed to cool to room temperature, and filtered through a cotton plug. The filter cake was washed with acetone (3 x 1 mL) and the combined organic phases were concentrated by under reduced pressure onto silica gel. The silica-loaded residue was purified by silica gel flash chromatography (19% EtOAc/hexanes) to give pyrimidinone **5c** as a colorless oil (101 mg, 83% yield): **^{1}H NMR (400 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 7.70 (br s, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 2H), 5.95 (ddt, *J* = 16.6, 10.3, 6.0 Hz, 1H), 5.38 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.32 (d, *J* = 10.4 Hz, 1H), 5.25 (m, 2H), 4.70 (d, *J* = 6.0 Hz, 2H), 4.41 (m, 1H), 3.62 (s, 3H), 3.47 (m, 1H), 2.58 (ddd, *J* = 16.0, 9.5, 6.4 Hz, 1H), 2.46 – 2.33 (m, 1H),

2.21 (ddd, *J* = 10.0, 6.3, 3.2 Hz, 2H), 1.48 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 173.0, 172.9, 169.7, 153.1, 134.9, 132.4, 131.1, 128.4, 128.3, 120.1, 82.2, 67.2, 58.3, 57.6, 55.6, 51.9, 48.7, 48.2, 29.7, 28.3; **IR (Neat Film, NaCl)** 2978, 1704, 1423, 1368, 1248, 1153, 987, 803, 722, 696 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{24}H_{31}N_2O_8$ $[M+H]^+$: 475.2075, found 475.2074.

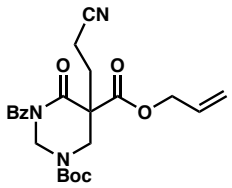


5-allyl 1-(tert-butyl) 3-benzoyl-5-(2-chloroallyl)-4-oxotetrahydropyrimidine-1,5(2H)-dicarboxylate (5d). To a suspension of allyl ester **SI-6** (200 mg, 0.51 mmol, 1.0 equiv) and tetrabutylammonium iodide (17 mg, 0.05 mmol, 0.1 equiv), in THF (5.1 mL) at 0 °C was added NaH (60% in mineral oil, 25 mg, 0.62 mmol, 1.2 equiv). After stirring for 30 min at 0 °C, 2,3-dichloro-1-propene (95 µL, 1.02 mmol, 2 equiv) was added and the reaction mixture heated at 40 °C for 16 h. The reaction was quenched with aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over anhydrous Na_2SO_4, decanted, and concentrated under reduced pressure onto silica gel. The silica-loaded residue was purified by silica gel flash chromatography (10% → 15% EtOAc/hexanes) to give 2-chloro-allyl allyl ester **5d** as a colorless oil (140 mg, 59% yield): **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.75 (d, *J* = 8.6 Hz, 2H), 7.51 (s, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 6.07 – 5.90 (m, 1H), 5.71 – 5.48 (m, 1H), 5.33 (m, 4H), 5.03 (d, *J* = 12.5 Hz, 1H), 4.85 – 4.43 (m, 3H), 3.58 (mz, 1H), 3.32 (d, *J* = 15.1 Hz, 1H), 3.03 (d, *J* = 15f.1 Hz, 1H), 1.48 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 173.3, 169.9, 168.7, 153.4, 136.3, 134.9, 132.4, 131.2, 128.7, 128.2, 120.1, 118.8, 82.1, 67.7, 58.5, 57.8, 55.1, 47.7, 47.2, 41.0, 28.3; **IR (Neat Film, NaCl)** 2978, 1703, 1632, 1478, 1450, 1423, 1368, 1289, 1246, 1137, 902, 803, 721, 695, 633 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{23}H_{28}ClN_2O_6$ $[M+H]^+$: 463.1630, found 463.1641.

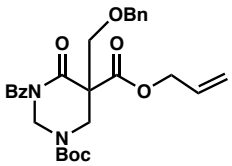


5-Allyl 1-(*tert*-butyl) 3-benzoyl-5-benzyl-4-oxotetrahydropyrimidine-1,5(2*H*)-dicarboxylate (5e). To a solution of allyl ester **SI-6** (100 mg, 0.26 mmol, 1.0 equiv) in THF (2.6 mL) at room temperature was added sodium hydride (11 mg, 0.28 mmol, 1.1 equiv). After stirring for 15 min, benzyl bromide (37 µL, 0.31 mmol, 1.2 equiv) was added. The reaction mixture was maintained at room temperature for 22 h and at 55 °C for 24 h. The reaction was quenched with aqueous NH_4Cl (2 mL) and diluted with EtOAc (2mL). The aqueous phase was extracted with EtOAc (3 x 3mL) and the combined organic phases were dried over anhydrous Na_2SO_4, decanted, and concentrated under reduced pressure onto silica gel. The silica-loaded residue was purified by silica gel flash chromatography (15% EtOAc/hexanes) to give benzylated allyl ester **5e** as a colorless oil (94 mg, 76%

yield): **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.71 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.29 – 7.19 (m, 3H), 7.14 (dd, *J* = 7.4, 2.2 Hz, 2H), 5.95 (ddt, *J* = 16.6, 10.4, 6.0 Hz, 1H), 5.44 – 5.19 (m, 3H), 4.73 (m, 3H), 4.56 – 4.37 (m, 1H), 3.50 (d, *J* = 14.0 Hz, 1H), 3.33 (d, *J* = 13.9 Hz, 1H), 3.14 (d, *J* = 14.0 Hz, 1H), 1.45 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 173.1, 170.4, 169.3, 153.2, 135.0, 134.9, 132.4, 131.3, 130.9, 128.7, 128.7, 128.2, 127.5, 119.9, 81.9, 67.3, 58.0, 57.5, 57.3, 47.8, 47.2, 38.1, 28.3; **IR (Neat Film, NaCl)** 3063, 2978, 2935, 1704, 1602, 1479, 1451, 1418, 1368, 1287, 1251, 1152, 1093, 1002, 927, 902, 857, 804, 764, 727, 697, 635 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{27}H_{31}N_2O_6$ $[M+H]^+$: 479.2177, found 479.2180.

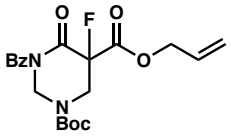


5-allyl 1-(tert-butyl) 3-benzoyl-5-(2-cyanoethyl)-4-oxotetrahydropyrimidine-1,5(2H)-dicarboxylate (5f). To a solution of allyl ester **SI-6** (100 mg, 0.26 mmol, 1.0 equiv) and acrylonitrile (34 μL, 0.52 mmol, 2.0 equiv) in acetonitrile (1.3 mL) at room temperature was added DBU (1.9 μL, 0.013 mmol, 0.05 equiv). After 22 h at room temperature, the reaction mixture was heated to 70 °C for 32 h, allowed to cool to room temperature, and treated with additional DBU (1.9 μL, 0.013 mmol, 0.05 equiv). After 2 h at 70 °C, the reaction mixture was allowed to cool to room temperature, directly concentrated onto silica gel, and purified by silica gel flash chromatography (22% EtOAc/hexanes) to give cyanoethylated pyrimidinone **5f** as a colorless oil (71.5 mg, 63% yield): **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.72 (d, *J* = 7.7 Hz, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 5.97 (ddt, *J* = 16.7, 10.3, 6.1 Hz, 1H), 5.41 (dd, *J* = 17.4, 1.5 Hz, 1H), 5.36 (d, *J* = 10.5 Hz, 1H), 5.28 (m, 2H), 4.74 (m, 2H), 4.41 (d, *J* = 13.8 Hz, 1H), 3.49 (d, *J* = 13.8 Hz, 1H), 2.72 (dt, *J* = 16.2, 7.9 Hz, 1H), 2.50 (dt, *J* = 16.6, 7.8 Hz, 1H), 2.20 (t, *J* = 7.9 Hz, 2H), 1.49 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 173.0, 169.4, 169.0, 153.1, 134.6, 132.7, 130.8, 128.4, 128.4, 120.6, 118.9, 82.6, 67.6, 67.6, 58.8, 57.9, 55.1, 49.0, 48.4, 29.2, 28.4, 13.6; **IR (Neat Film, NaCl)** 2979, 2250, 1698, 1450, 1423, 1369, 1286, 1250, 1155, 1030, 939, 857, 803, 718, 696, 635 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{23}H_{31}N_4O_6$ $[M+NH_4]^+$: 459.2238, found 459.2243.

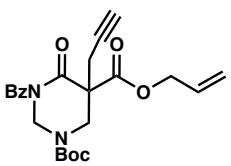


5-allyl 1-(tert-butyl) 3-benzoyl-5-((benzyloxy)methyl)-4-oxotetrahydropyrimidine-1,5(2H)-dicarboxylate (5g). Following the procedure described for the preparation of **5a**, allyl ester **SI-6** (200 mg, 0.52 mmol, 1.0 equiv) was treated with sodium hydride (29 mg, 0.72 mmol, 1.4 equiv) and alkylated with benzyl chloromethyl ether (127 μL, 0.93 mmol,

1.8 equiv) to give, after two rounds of purification by silica gel flash chromatography (dry load SiO_2, 16 → 25% EtOAc/hexanes), BOM-alkylated allyl ester **5g** as a colorless oil (57 mg, 22% yield): **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.73 (t, *J* = 8.3 Hz, 2H), 7.50 (t, *J* = 7.9 Hz, 1H), 7.41 – 7.24 (m, 7H), 5.94 (ddt, *J* = 16.5, 10.3, 6.0 Hz, 1H), 5.63 (d, *J* = 12.2 Hz, 1H), 5.43 – 5.25 (m, 2H), 4.95 (d, *J* = 12.4 Hz, 1H), 4.74 (dd, *J* = 13.0, 5.9 Hz, 1H), 4.70 – 4.36 (m, 4H), 4.07 (d, *J* = 9.2 Hz, 1H), 3.96 – 3.80 (m, 1H), 3.74 (d, *J* = 9.3 Hz, 1H), 1.48 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 173.2, 169.0, 168.7, 168.3, 153.6, 153.3, 137.5, 134.9, 132.2, 131.3, 131.0, 128.6, 128.1, 128.0, 127.7, 119.9, 119.7, 81.9, 73.9, 70.0, 67.1, 58.7, 57.9, 57.0, 47.0, 46.7, 28.3; **IR (Neat Film, NaCl)** 2978, 2360, 1704, 1453, 1418, 1368, 1290, 1248, 1153, 1128, 1072, 1003, 904, 857, 803, 735, 697, 633 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{28}H_{33}N_2O_7$ $[M+H]^+$: 509.2282, found 509.2279.



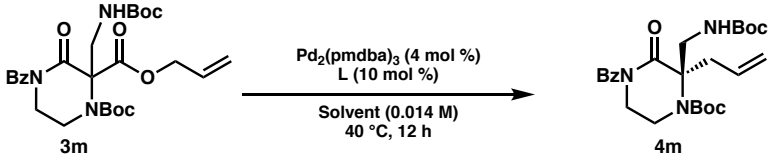
5-allyl 1-(tert-butyl) 3-benzoyl-5-fluoro-4-oxotetrahydropyrimidine-1,5(2H)-dicarboxylate (5h). To a solution of allyl ester **SI-6** (100 mg, 0.257 mmol, 1.0 equiv) in THF (2.6 mL) at room temperature was added sodium hydride (11 mg, 0.28 mmol, 1.1 equiv). After stirring for 15 min, Selectfluor (109 mg, 0.31 mmol, 1.2 equiv) was added and the reaction mixture was stirred for 1.5 h at room temperature. The reaction was quenched with aqueous NH_4Cl (2 mL) and diluted with EtOAc (2 mL). The aqueous phase was extracted with EtOAc (3 x 3 mL) and the combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated by reduced pressure onto silica gel. The residue was purified by silica gel flash chromatography (4:1 hexanes/EtOAc) to give fluorinated allyl ester **5h** as a colorless oil (92 mg, 0.226 mmol, 88%); **^{1}H NMR (400 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 7.67 (s, 2H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 5.95 (ddt, *J* = 16.6, 10.3, 6.0 Hz, 1H), 5.63 – 5.07 (m, 4H), 4.88 – 4.77 (m, 1H), 4.75 (s, 1H), 4.43 (m, 1H), 3.99 (m, 1H), 1.49 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 172.4, 165.3, 164.4, 153.1, 133.8, 132.9, 130.5, 128.6, 128.5, 120.4, 89.3 (d, J_{CF} = 192.9 Hz, appears as four peaks due to the presence of two rotamers and coupling with fluorine), 82.8, 67.8, 59.0, 58.4, 49.2, (d, J_{CF} = 28.3 Hz), 48.4 (d, J_{CF} = 27.3 Hz), 28.2; **IR (Neat Film, NaCl)** 2979, 2360, 1770, 1715, 1601, 1478, 1450, 1418, 1369, 1287, 1252, 1157, 1134, 1072, 1018, 907, 857, 829, 803, 764, 730, 695, 658, 633 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{20}H_{27}FN_3O_6$ $[M+NH_4]^+$: 424.1878, found 424.1877.



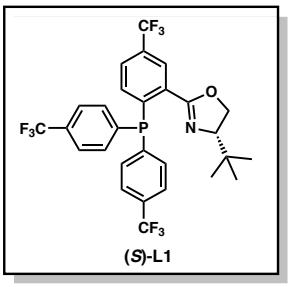
5-allyl 1-(tert-butyl) 3-benzoyl-4-oxo-5-(prop-2-yn-1-yl)tetrahydropyrimidine-1,5(2H)-dicarboxylate 5i. To a solution of allyl ester **SI-6** (200 mg, 0.51 mmol, 1.0 equiv) in THF (5 mL) at 0 °C was quickly added sodium hydride (23 mg, 0.57 mmol, 1.1 equiv). After stirring at 0 °C for 30 minutes, propargyl bromide (111 μL, 1.03 mmol, 2 equiv) was added and the reaction mixture was heated to 50 °C. After three hours, more propargyl bromide (111 μL, 1.03 mmol, 2 equiv) was added and the reaction was allowed to continue for 16 h at 50 °C. The reaction was quenched with aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over anhydrous Na_2SO_4, decanted, and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (50% CH_2Cl_2/hexanes → 70% CH_2Cl_2/hexanes → 20% EtOAc/hexanes) to afford the propargylated allyl ester **5i** as a colorless oil (160 mg, 73% yield): **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.74 (s, 2H), 7.50 (d, *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 5.96 (dd, *J* = 17.0, 10.6 Hz, 1H), 5.64 (dd, *J* = 12.4, 2.1 Hz, 1H), 5.39 (d, *J* = 17.2 Hz, 1H), 5.33 (d, *J* = 10.4 Hz, 1H), 5.16 – 4.88 (m, 1H), 4.82 – 4.32 (m, 3H), 4.01 – 3.63 (m, 1H), 3.03 (d, *J* = 18.2 Hz, 1H), 2.71 (dd, *J* = 17.0, 2.7 Hz, 1H), 2.09 (t, *J* = 2.6 Hz, 1H), 1.49 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 173.3, 169.6, 168.6, 153.5, 134.9, 132.4, 131.2, 130.9, 128.6, 128.2, 120.0, 82.2, 78.8, 72.6, 67.5, 58.9, 58.2, 55.2, 48.2, 28.3, 23.0; **IR (Neat Film, NaCl)** 3280, 2978, 1704, 1600, 1479, 1450, 1422, 1368, 1287, 1245, 1155, 1140, 1073, 1016, 929, 904, 856, 803, 765, 733 695, 656 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{23}H_{27}N_2O_6$ $[M+H]^+$: 427.1864, found 427.1859.

General Procedure for Allylic Alkylation Optimization Screen

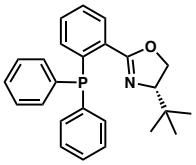
Table 1. Optimization of Reaction Parameters



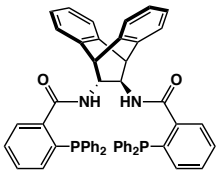
Entry	L	Solvent	Yield (%)[b]	ee (%)[c]
1	L1	Tol	75	76
2	L2	Tol	70	1
3	L3	Tol	83	52
4	L1	THF	–	13
5	L1	MTBE	–	80
6	L1	2:1 Hex/Tol	93	93



(*S*)-L1



(*S*)-L2



(*S,S*)-L3

[a] Screens performed on a 0.04 mmol scale. All reported yields are for isolated products. The ee values were determined by chiral SFC analysis. Bz = benzoyl, Boc = tert-butoxycarbonyl, pmdba = bis(4-methoxybenzylidene)acetone

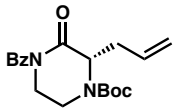
In a nitrogen-filled glovebox, an oven-dried 1 dram vial was charged with $Pd_2(pmdba)_3$ (1.7 mg, 0.0015 mmol, 4 mol %), ligand (10 mol %), solvent (1 mL), and a magnetic stir bar. The vial was stirred at ambient glovebox temperature (27 °C) for 30 min and then substrate **3m** (20 mg, 0.04 mmol, 1.0 equiv) was added as a solution in solvent (1.8 mL, total concentration 0.014 M). The vial was sealed with a teflon cap and heated to 40 °C. When complete consumption of the starting material was observed by thin layer chromatography, the reaction mixture was removed from the glovebox and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography to afford the oxopiperazine **4m**.

General Procedure for Pd-Catalyzed Decarboxylative Allylic Alkylation Reactions

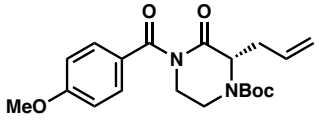
Please note The absolute configuration for all other products has been inferred by analogy.[1] For respective SFC conditions, please refer to the section **Determination of Enantiomeric Excess (S**.

In a nitrogen-filled glovebox, an oven-dried 1 dram vial or 20 mL scintillation vial was charged with $Pd_2(pmdba)_3$ or $Pd_2(dba)_3$ (4 mol %), (*S*)-$(CF_3)_3$-*t*Bu-PHOX (10 mol %), hexane/toluene (2:1), and a magnetic stir bar. The vial was stirred at ambient glovebox temperature (27 °C) for 30 min and then the substrate (1.0 equiv) was added as a solution in hexane/toluene (2:1, total concentration 0.014 M or 0.033 M). The vial was sealed with a teflon cap and heated to 40 °C. When complete consumption of the starting material was observed by thin layer chromatography, the reaction mixture was removed from the glovebox and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography to afford the desired oxopiperazine.

Experimental Procedures and Spectroscopic data for the Pd-Catalyzed Decarboxylative Asymmetric Allylic Alkylation of Piperazinone Substrates

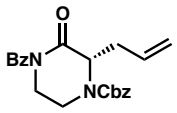


***tert*-butyl (*S*)-2-allyl-4-benzoyl-3-oxopiperazine-1-carboxylate (4a)**. Following the general procedure, allyl ester **3a** (25 mg, 0.064 mmol, 1.0 equiv) in toluene (1.45 mL) was added to a solution of $Pd_2(dba)_3$ (2.3 mg, 0.0026 mmol, 4 mol %) and (*S*)-$(CF_3)_3$-*t*Bu-PHOX (3.8 mg, 0.0064 mmol, 10 mol %) in toluene (0.5 mL). Purification by flash chromatography (20% EtOAc/hexanes) gave monosubstituted oxopiperazine **4a** as a yellow oil (21 mg, 90% yield, 92% ee). **^{1}H NMR (400 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 7.64 – 7.46 (m, 3H), 7.41 (m, 2H), 5.83 (ddt, *J* = 17.2, 10.0, 7.3 Hz, 1H), 5.22 – 5.07 (m, 2H), 4.70 (m, 1H), 4.45 – 3.99 (m, 1H), 3.99 – 3.70 (m, 2H), 3.42 (m, 1H), 2.90 – 2.52 (m, 2H), 1.50 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 173.6, 170.6, 153.8, 135.3, 133.2, 132.2, 128.3, 128.3, 119.0, 81.3, 58.4, 44.5, 38.1, 37.2, 28.5. **IR (Neat Film, NaCl)** 2977, 2930, 1692, 1600, 1450, 1413, 1392, 1366, 1300, 1231, 1159, 1130, 1008, 973, 920, 856, 795, 762, 729, 696, 656 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{19}H_{25}N_2O_4$ $[M+H]^+$: 345.1809, found 345.1810; **$[\alpha]_D^{23.0}$** +49.5 (c 1.00, $CHCl_3$); **SFC conditions**: 15% IPA, 2.5 mL/min, Chiralpak AD–H column, λ = 210 nm, t_R (min): major = 3.741, minor = 2.682.

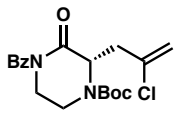


***tert*-butyl (*S*)-2-allyl-4-(4-methoxybenzoyl)-3-oxopiperazine-1-carboxylate (4b)**.

Following the general procedure, anisoyl-protected allyl ester **3b** (15 mg, 0.036 mmol, 1.0 equiv) in toluene (0.6 mL) was added to a solution of $Pd_2(dba)_3$ (1.7 mg, 0.0014 mmol, 4 mol %) and (*S*)-$(CF_3)_3$-*t*Bu-PHOX (2.8 mg, 0.0036 mmol, 10 mol %) in toluene (0.5 mL). Purification by flash chromatography (20% EtOAc/hexanes) gave monosubstituted oxopiperazine **4b** as a light yellow oil (12 mg, 92% yield, 96% ee): **^{1}H NMR (400 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 7.60 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 5.85 (ddt, *J* = 17.1, 10.0, 7.3 Hz, 1H), 5.24 – 5.04 (m, 2H), 4.69 (m, 1H), 4.19 (m, 1H), 3.85 (m, 5H), 3.42 (m, 1H), 2.89 – 2.56 (m, 2H), 1.49 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.0, 170.6, 163.3, 153.9, 133.4, 131.2, 127.1, 118.9, 113.7, 81.3, 58.4, 55.6, 44.6, 38.3, 37.4, 28.5; **IR (Neat Film, NaCl)** 2976, 1694, 1605, 1512, 1462, 1416, 1366, 1315, 1257, 1234, 1170, 1130, 1003, 973, 842, 770 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{20}H_{27}N_2O_5$ $[M+H]^+$: 375.1914, found 375.1931; **$[\alpha]_D^{23.0}$** +41.7 (c 1.00, $CHCl_3$); **SFC conditions**: 15% IPA, 2.5 mL/min, Chiralpak AD–H column, λ = 210 nm, t_R (min): major = 4.708, minor = 3.998.

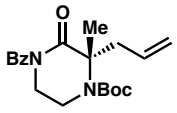


benzyl (*S*)-2-allyl-4-benzoyl-3-oxopiperazine-1-carboxylate (4c). Following the general procedure, Cbz-protected allyl ester **3c** (20 mg, 0.047 mmol, 1.0 equiv) in toluene (0.9 mL) was added to a solution of $Pd_2(dba)_3$ (2.2 mg, 0.0019 mmol, 4 mol %) and (*S*)-$(CF_3)_3$-*t*Bu-PHOX (3.5 mg, 0.0047 mmol, 10 mol %) in toluene (0.5 mL). Purification by flash chromatography (20% EtOAc/hexanes) gave monosubstituted oxopiperazine **4c** as a colorless oil (15 mg, 83% yield, 99% ee): **^{1}H NMR (500 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 7.62 – 7.46 (m, 3H), 7.44 – 7.29 (m, 7H), 5.79 (m, 1H), 5.16 (m, 4H), 4.83 (m, 1H), 4.26 (m, 1H), 3.97 (m, 1H), 3.87 (m, 1H), 3.49 (m, 1H), 2.89 – 2.53 (m, 2H**); ^{13}C NMR (126 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 173.5, 170.2, 154.7, 136.0, 135.2, 132.9, 132.3, 128.8, 128.6, 128.6, 128.4, 128.3, 119.3, 68.0, 58.4, 44.3, 39.6, 38.9, 37.2, 36.9; **IR (Neat Film, NaCl)** 3065, 2951, 1702, 1600, 1449, 1427, 1395, 1362, 1302, 1228, 1163, 1127, 1015, 975, 922, 796, 761,730, 697, 656 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{22}H_{23}N_2O_4$ $[M+H]^+$: 379.1652, found 379.1659; **$[\alpha]_D^{23.0}$** +66.0 (c 1.0, $CHCl_3$); **SFC conditions**: 30% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): major = 4.873, minor = 6.748.

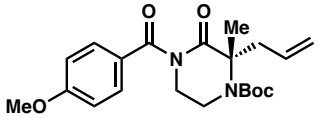


***tert*-butyl (*S*)-4-benzoyl-2-(2-chloroallyl)-3-oxopiperazine-1-carboxylate (4d)**. Following the general procedure, 2-chloroallyl ester **3d** (20 mg, 0.047 mmol, 1.0 equiv.) in hexanes/toluene (2:1, 1.9 mL) was added to a solution of $Pd_2(pmdba)_3$ (2.1 mg, 0.0019 mmol, 4 mol %) and (*S*)-$(CF_3)_3$-*t*Bu-PHOX (2.8 mg, 0.0047 mmol, 10 mol %) in

hexanes/toluene (2:1, 1.5 mL). Purification by silica gel flash chromatography (15% EtOAc/hexanes) gave oxopiperazine **4d** as a light yellow oil (15 mg, 85% yield, 98% ee). **^{1}H NMR (400 MHz, $CDCl_3$)** δ (A mixture of two rotamers) 7.56 (d, *J* = 7.8 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 5.30 (s, 1H), 5.24 (s, 1H), 5.06 – 4.88 (m, 1H), 4.40 – 4.06 (m, 1H), 3.94 (m, 1H), 3.84 (m, 1H), 3.55 – 3.29 (m, 1H), 2.95 (dd, *J* = 13.1, 7.4 Hz, 2H), 1.51 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.5, 169.8, 153.7, 137.5, 135.3, 132.3, 128.4, 128.3, 116.8, 81.9, 57.0, 44.6, 41.8, 37.7, 28.4. **IR (Neat Film, NaCl)** 2977, 2359, 1694, 1635, 1456, 1418, 1394, 1367, 1284, 1232, 1200, 1158, 1007, 971, 892, 856, 796, 730, 696 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{19}H_{24}ClN_2O_4$ $[M+H]^+$: 379.1419, found 379.1416; **$[\alpha]_D^{23.1}$** +33.8 (c 1.00, $CHCl_3$); **SFC conditions**: 15% IPA, 2.5 mL/min, Chiralpak AD–H column, λ = 254 nm, t_R (min): major = 4.482, minor = 3.224.

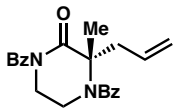


***tert*-butyl (*S*)-2-allyl-4-benzoyl-2-methyl-3-oxopiperazine-1-carboxylate (4e).** Following the general procedure, methylated allyl ester **3e** (23 mg, 0.057 mmol, 1.0 equiv) in toluene (1.2 mL) was added to a solution of $Pd_2(pmdba)_3$ (2.7 mg, 0.0023 mmol, 4 mol %) and (*S*)-$(CF_3)_3$-*t*Bu-PHOX (3.7 mg, 0.0057 mmol, 10 mol %) in toluene (0.5 mL). Purification by flash chromatography (15% EtOAc/hexanes) gave di-substituted oxopiperazine **4e** as a light yellow oil (17 mg, 85% yield, 96% ee). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.57 – 7.46 (m, 3H), 7.40 (t, J = 7.6 Hz, 2H), 5.81 – 5.67 (m, 1H), 5.17 – 5.13 (m, 1H), 5.12 (d, *J* = 1.1 Hz, 1H), 4.16 – 4.02 (m, 1H), 4.03 – 3.91 (m, 1H), 3.79 (ddd, *J* = 12.9, 9.0, 3.0 Hz, 1H), 3.53 (ddd, *J* = 14.1, 9.0, 2.8 Hz, 1H), 3.11 (m, 1H), 2.84 – 2.70 (m, 1H), 1.77 (s, 3H), 1.53 (s, 9H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.3, 172.8, 135.8, 133.1, 131.8, 128.3, 127.6, 119.5, 81.2, 67.3, 44.2, 42.7, 41.0, 28.6, 25.5; **IR (Neat Film, NaCl)** 3076, 2977, 2934, 1692, 1641, 16001,102, 1450, 1392, 1366, 1301, 1230, 1166, 1106, 1047, 1016, 955, 922, 852, 790, 757, 727, 695 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{20}H_{27}N_2O_4$ $[M+H]^+$: 359.1965, found 359.1966; **$[\alpha]_D^{22.8}$** +6.5 (c 2.0, $CHCl_3$); **SFC conditions**: 7% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 7.208, minor = 4.714.

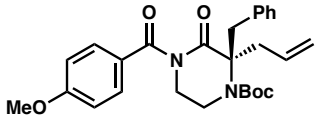


***tert*-butyl (*S*)-2-allyl-4-(4-methoxybenzoyl)-2-methyl-3-oxopiperazine-1-carboxylate (4f)**. Following the general procedure, anisoyl-protected allyl ester **3f** (25 mg, 0.058 mmol, 1.0 equiv) in toluene (1.3 mL) was added to a solution of $Pd_2(pmdba)_3$ (2.5 mg, 0.0023 mmol, 4 mol %) and (*S*)-$(CF_3)_3$-*t*Bu-PHOX (3.4 mg, 0.0058 mmol, 10 mol %) in toluene (0.5 mL). Purification by flash chromatography (20% EtOAc/hexanes) gave di-substituted oxopiperazine **4f** as a light pink oil (19 mg, 86% yield, 96% ee). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.70 – 7.53 (m, 2H), 6.99 – 6.82 (m, 2H), 5.86 – 5.67 (m, 1H), 5.23 – 5.04 (m,

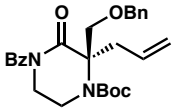
2H), 4.01 (dddd, *J* = 33.5, 13.9, 5.8, 2.8 Hz, 2H), 3.85 (s, 3H), 3.74 (ddd, *J* = 12.7, 9.0, 2.8 Hz, 1H), 3.52 (ddd, *J* = 13.9, 9.0, 2.7 Hz, 1H), 3.20 (s, 1H), 2.80 (ddt, *J* = 14.0, 7.1, 1.2 Hz, 1H), 1.77 (s, 3H), 1.52 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.1, 172.4, 163.0, 153.9, 133.2, 130.6, 127.5, 119.4, 113.6, 81.2, 67.1, 55.5, 44.2, 42.8, 41.1, 28.6, 25.6; **IR (Neat Film, NaCl)** 3076, 2977, 2934, 1692, 1641, 16001,102, 1450, 1392, 1366, 1301, 1230, 1166, 1106, 1047, 1016, 955, 922, 852, 790, 757, 727, 695 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{21}H_{29}N_2O_5$ $[M+H]^+$: 389.2071, found 389.2083; **$[\alpha]_D^{22.0}$** +75.6 (c 2.9, $CHCl_3$); **SFC conditions**: 10% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 5.370, minor = 4.278.



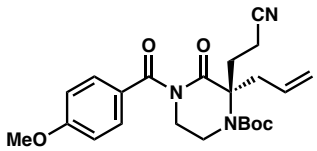
***tert*-butyl (*S*)-2-allyl-4-(4-methoxybenzoyl)-2-methyl-3-oxopiperazine-1-carboxylate (4g)**. Following the general procedure, di-Bz-protected allyl ester **3g** (10 mg, 0.025 mmol, 1.0 equiv) in toluene (1.3 mL) was added to a solution of $Pd_2(dba)_3$ (0.9 mg, 0.00098 mmol, 4 mol %) and (*S*)-$(CF_3)_3$-*t*Bu-PHOX (1.5 mg, 0.0025 mmol, 10 mol %) in toluene (0.5 mL). Purification by flash chromatography (20% EtOAc/hexanes) gave di-substituted oxopiperazine **4f** as a colorless oil (8 mg, 89% yield, 70% ee). Product identity matched previously reported characterization data.[4] **SFC conditions**: 10% MeOH, 2.5 mL/min, Chiralpak OJ-H column, λ = 254 nm, t_R (min): major = 5.574, minor = 6.659.



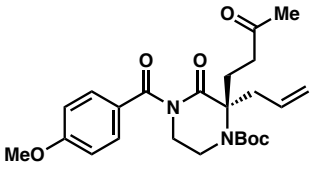
***tert*-butyl (*R*)-2-allyl-2-benzyl-4-(4-methoxybenzoyl)-3-oxopiperazine-1-carboxylate (4h).** Following the general procedure, benzylated allyl ester **3h** (10 mg, 0.02 mmol, 1.0 equiv) in hexanes/toluene (2:1, 0.9 mL) was added to a solution of $Pd_2(pmdba)_3$ (0.86 mg, 0.00078 mmol, 4 mol %) and (*S*)-$(CF_3)_3$-*t*Bu-PHOX (1.2 mg, 0.002 mmol, 10 mol %) in hexanes/toluene (2:1, 0.5 mL). Purification by flash chromatography (5% → 10% → 15% EtOAc/hexanes) gave di-substituted oxopiperazine **4h** as a colorless oil (7 mg, 77% yield, 96% ee): **^{1}H NMR (400 MHz, $CDCl_3$)** δ (A mixture of two rotamers) 7.57 (t, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 5.7 Hz, 3H), 7.22 – 7.07 (m, 2H), 6.91 (d, *J* = 8.3 Hz, 2H), 5.82 (ddt, *J* = 17.0, 9.6, 7.1 Hz, 1H), 5.29 – 5.13 (m, 2H), 3.88 (m, 4H), 3.74 – 3.45 (m, 2H), 3.31 (m, 1H), 3.16 (d, *J* = 12.0 Hz, 2H), 2.98 – 2.57 (m, 2H), 1.57 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (A mixture of two rotamers) 172.7, 172.3, 172.0, 163.2, 154.7, 153.4, 137.1, 136.4, 133.1, 132.6, 131.3, 130.4, 128.7, 128.5, 127.5, 127.2, 119.9, 119.7, 113.5, 82.2, 80.6, 71.7, 55.6, 43.6, 43.3, 42.9, 42.6, 41.8, 29.8, 28.9, 28.6; **IR (Neat Film, NaCl)** 2975, 1691, 1604, 1512, 1454, 1365,1309, 1282, 1258, 1167, 1104, 1077, 1021, 993, 925, 839, 768, 740, 704cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{27}H_{33}N_2O_5$ $[M+H]^+$: 465.2384, found 465.2390; **$[\alpha]_D^{23.4}$** +31.0 (c 0.47, $CHCl_3$); **SFC conditions**: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): major = 7.471, minor = 5.802.



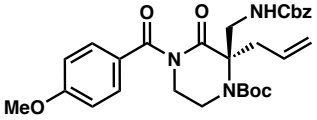
***tert*-butyl (*R*)-2-allyl-4-benzoyl-2-((benzyloxy)methyl)-3-oxopiperazine-1-carboxylate (4i).** (Following the general procedure, benzyloxy methyl ether allyl ester **3i** (25 mg, 0.049 mmol, 1.0 equiv) in hexanes/toluene (2:1, 3.0 mL) was added to a solution of $Pd_2(pmdba)_3$ (2.2 mg, 0.0020 mmol, 4 mol %) and (*S*)-$(CF_3)_3$-*t*Bu-PHOX (2.9 mg, 0.0049 mmol, 10 mol %) in hexanes/toluene (2:1, 0.5 mL). Purification by flash chromatography (15% EtOAc/hexanes) gave di-substituted oxopiperazine **4i** as a colorless oil (20 mg, 87% yield, 92% ee): **^{1}H NMR (500 MHz, $CDCl_3$)** δ (A mixture of two rotamers) 7.61 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.51 – 7.43 (m, 1H), 7.38 – 7.26 (m, 7H), 5.72 (ddt, *J* = 17.6, 10.3, 7.4 Hz, 1H), 5.21 – 5.09 (m, 2H), 4.57 (t, *J* = 13.3 Hz, 3H), 4.32 – 3.63 (m, 5H), 3.25 – 2.93 (m, 1H), 2.60 (br s, 1H), 1.50 (s, 9H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 173.3, 172.5, 153.4, 135.6, 132.1, 131.9, 128.6, 128.3, 128.2, 127.9, 127.5, 120.0, 75.1, 74.2, 73.7, 70.6, 43.5, 38.5, 37.0, 28.6; **IR (Neat Film, NaCl)** 3064, 2976, 2931, 1692, 1601, 1474, 1452, 1392, 1365, 1317, 1286, 1251, 1232, 1164, 1102, 1062, 1016, 969, 924, 857, 730, 696, 671 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{27}H_{33}N_2O_5$ $[M+H]^+$: 465.2384, found 465.2388; **$[\alpha]_D^{23.8}$** –13.9 (c 0.33, $CHCl_3$); **SFC conditions**: 7% IPA, 2.5 mL/min, Chiralpak OJ-H column, λ = 254 nm, t_R (min): major = 3.737, minor = 4.398.



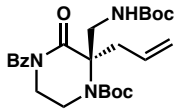
***tert*-butyl (*S*)-2-allyl-2-(2-cyanoethyl)-4-(4-methoxybenzoyl)-3-oxopiperazine-1-carboxylate (4j)**. Following the general procedure, *α*-cyanoethylated allyl ester **3j** (25 mg, 0.053 mmol, 1.0 equiv) in hexanes/toluene (2:1, 2.8 mL) was added to a solution of $Pd_2(dba)_3$ (1.9 mg, 0.0021 mmol, 4 mol %) and (*S*)-$(CF_3)_3$-*t*Bu-PHOX (3.1 mg, 0.0053 mmol, 10 mol %) in hexanes/toluene (2:1, 1.0 mL). Purification by silica gel flash chromatography (dry load SiO_2, 3:1 hexanes/EtOAc) gave oxopiperazine **4j** as a colorless oil (20 mg, 88% yield, 97% ee): **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.63 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 5.79 (ddt, *J* = 16.6, 10.4, 7.5 Hz, 1H), 5.24 (d, *J* = 1.7 Hz, 1H), 5.20 (dd, *J* = 9.9, 1.9 Hz, 1H), 3.98 – 3.87 (m, 2H), 3.86 (s, 3H), 3.84 – 3.71 (m, 2H), 3.27 (m, 1H), 2.82 (m, 1H), 2.69 (dd, *J* = 13.8, 7.4 Hz, 1H), 2.47 (dt, *J* = 14.1, 7.4 Hz, 1H), 2.32 (t, *J* = 7.2 Hz, 2H), 1.53 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.4, 171.5, 163.4, 153.6, 132.0, 131.2, 127.0, 120.6, 119.1, 113.7, 82.0, 69.0, 55.6, 43.8, 43.2, 42.0, 32.3, 28.5, 13.1; **IR (Neat Film, NaCl)** 2976, 2933, 2359, 2247, 1694, 1605, 1579, 1512, 1456, 1366, 1281, 1258 1168, 1113, 1020, 974, 928, 843, 768, 614 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{23}H_{30}N_3O_5$ $[M+H]^+$: 428.2180, found 428.2182; **$[\alpha]_D^{23.2}$** –4.3 (c 1.0, $CHCl_3$); **SFC conditions**: 15% IPA, 2.5 mL/min, Chiralpak OD-H column, λ = 210 nm, t_R (min): major = 6.049, minor = 5.143.



***tert*-butyl (*S*)-2-allyl-4-(4-methoxybenzoyl)-3-oxo-2-(3-oxobutyl)piperazine-1-carboxylate (4k).** Following the general procedure, ketone **3k** (25 mg, 0.051 mmol, 1.0 equiv) in hexanes/toluene (2:1, 2.2 mL) was added to a solution of $Pd_2(dba)_3$ (1.9 mg, .002 mmol, 4 mol %) and (*S*)-$(CF_3)_3$-*t*Bu-PHOX (3.0 mg, 0.0051 mmol, 10 mol %) in hexanes/toluene (2:1, 1.5 mL). Purification by silica gel flash chromatography (dry load SiO_2, 30% EtOAc/hexanes) gave ketone **4k** as a pale yellow oil (17 mg, 73% yield, 97% ee); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.59 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 5.79 (ddt, *J* = 14.6, 9.4, 7.5 Hz, 1H), 5.18 (dd, *J* = 13.8, 1.9 Hz, 2H), 3.92 – 3.81 (m, 6H), 3.80 – 3.66 (m, 1H), 3.22 (s, 1H), 2.74 (dd, *J* = 13.8, 7.3 Hz, 1H), 2.72, (m, 1H), 2.50 – 2.27 (m, 3H), 2.13 (s, 3H), 1.51 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 207.5, 172.6, 172.4, 163.2, 132.8, 131.0, 127.3, 120.0, 113.6, 81.6, 69.5, 55.6, 43.9, 43.2, 39.1, 32.3, 30.0, 28.6, 24.8; **IR (Neat Film, NaCl)** 2975, 1694, 1605, 1512, 1456, 1392, 1366, 1282, 1258, 1168, 1113, 1062, 1019, 974, 923, 841, 768 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{24}H_{33}N_2O_6$ $[M+H]^+$: 445.2333, found 445.2335; **$[\alpha]_D^{23.2}$** +25.1 (c 0.97, $CHCl_3$); **SFC conditions**: 7% IPA, 2.5 mL/min, Chiralpak OD-H column, λ = 235 nm, t_R (min): major = 9.712, minor = 10.434.

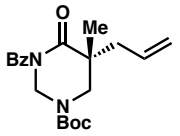


***tert*-butyl (*R*)-2-allyl-2-((((benzyloxy)carbonyl)amino)methyl)-4-(4-methoxybenzoyl)-3-oxopiperazine-1-carboxylate (4l)**. Following the general procedure, aminomethyl allyl ester **3l** (100 mg, 0.17 mmol, 1.0 equiv) in hexanes/toluene (2:1, 10 mL) was added to a solution of $Pd_2(dba)_3$ (6.3 mg, 0.0069 mmol, 4 mol %) and (*S*)-$(CF_3)_3$-*t*Bu-PHOX (10 mg, 0.017 mmol, 10 mol %) in hexanes/toluene (2:1, 2 mL). Purification by silica gel flash chromatography (15% → 20% → 30% EtOAc/hexanes) gave di-substituted oxopiperazine **4l** as a yellow oil (60 mg, 65% yield, 92% ee); **^{1}H NMR (400 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 7.64 (t, *J* = 8.9 Hz, 2H), 7.44 – 7.23 (m, 5H), 6.89 (d, *J* = 8.5 Hz, 2H), 5.79 (dq, *J* = 16.8, 7.8 Hz, 1H), 5.32 – 4.93 (m, 5H), 4.31 – 3.97 (m, 1H), 3.95 – 3.64 (m, 7H), 3.64 – 3.45 (m, 1H), 3.45 – 2.87 (m, 1H), 2.64 (dd, *J* = 14.0, 7.3 Hz, 1H), 1.48 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.6, 172.3, 163.1, 156.4, 153.7, 136.6, 132.2, 131.1, 128.6, 128.4, 128.3, 127.3, 120.1, 113.6, 70.2, 67.0, 55.6, 46.9, 43.8, 43.2, 39.6, 28.6; **IR (Neat Film, NaCl)** 3357, 2975, 2361, 1694, 1605, 1512, 1456, 1366, 1317, 1283, 1255, 1169, 1094, 1061, 1020, 923, 841, 768, 699 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{29}H_{36}N_3O_7$ $[M+H]^+$: 538.2548, found 538.2543; **$[\alpha]_D^{22.8}$** +3.74 (c 2.0, $CHCl_3$); **SFC conditions:** 15% IPA, 2.5 mL/min, Chiralpak OD-H column, λ = 280 nm, t_R (min): major = 8.425, minor = 7.817.



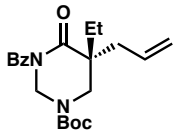
***tert*-Butyl (*R*)-2-allyl-4-benzoyl-2-(((tert-butoxycarbonyl)amino)methyl)-3-oxopiperazine-1-carboxylate (4m)**. Following the general procedure, allyl ester **3m** (100 mg, 0.19 mmol, 1.0 equiv) in hexanes/toluene (2:1, 8.0 mL) was added to a solution of $Pd_2(pmdba)_3$ (8.5 mg, 0.0077 mmol, 4 mol %) and (*S*)-$(CF_3)_3$-*t*Bu-PHOX (11.4 mg, 0.019 mmol, 10 mol %) in hexanes/toluene (2:1, 4.0 mL). Purification by flash chromatography (15% EtOAc/hexanes) gave di-substituted oxopiperazine **4m** as a pale yellow foam (85 mg, 93% yield, 93% ee): **^{1}H NMR (400 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 7.61 (d, *J* = 7.6 Hz, 2H), 7.51 (tt, *J* = 7.5, 2.1 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 5.91 – 5.66 (m, 1H), 5.19 (d, *J* = 15.6 Hz, 2H), 4.73 (s, 1H), 4.09 – 3.72 (m, 5H), 3.67 (dd, *J* = 14.0, 7.0 Hz, 1H), 3.43 – 2.97 (m, 1H), 2.72 – 2.51 (m, 1H), 1.54 (s, 9H), 1.43 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** 172.9, 172.8, 155.7, 153.6, 135.8, 132.3, 131.9, 128.2, 128.0, 120.1, 81.2, 79.7, 70.5, 46.5, 43.7, 43.2, 39.4, 28.6, 28.5; **IR (Neat Film, NaCl):** = 3374, 2977, 1694, 1504, 1454, 1392, 1366, 1317, 1286, 1231, 1165, 1094, 1060, 1014, 921, 855, 765, 729, 696 cm^{-1}; **HRMS (MM: ESI-APCI)**: m/z calc'd for $C_{25}H_{36}N_3O_6$ $[M+H]^+$: 474.2599, found: 474.2602; **$[\alpha]_D^{23.2}$** +2.7 (c 1.00, CH_3Cl); **SFC conditions**: 10% IPA, 2.5 mL/min, Chiralpak OD-H column, λ = 254 nm, t_R (min): major = 4.429, minor = 3.910.

Experimental Procedures and Spectroscopic Data for the Pd-Catalyzed Decarboxylative Asymmetric Allylic Alkylation of Tetrahydropyrimidinone Substrates

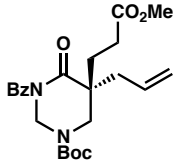


***tert*-butyl (*R*)-5-allyl-3-benzoyl-5-methyl-4-oxotetrahydropyrimidine-1(2H)-carboxylate (6a).** Following the general procedure, methylated pyrimidinone **5a** (15 mg, 0.037 mmol, 1.0 equiv) in hexanes/toluene (2:1, 1.0 mL) was added to a solution of $Pd_2(pmdba)_3$ (1.6 mg, 0.0015 mmol, 4 mol %) and (*S*)-$(CF_3)_3$-*t*Bu-PHOX (2.2 mg, 0.0037 mmol, 10 mol %) in hexanes/toluene (2:1, 1.7 mL). Purification by silica gel flash chromatography (13% EtOAc/hexanes) gave *α*-methyl pyrimidinone **6a** as a colorless oil (11 mg, 83% yield, 93% ee): **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.57 – 7.46 (m, 3H), 7.40 (t, *J* = 7.6 Hz, 2H), 5.78 (dq, *J* = 16.9, 8.0 Hz, 1H), 5.31 (d, *J* = 8.4 Hz, 1H), 5.25 – 5.09 (m, 3H), 3.69 (d, *J* = 13.8 Hz, 1H), 3.55 (m, 1H), 2.52 (m, 1H), 2.31 (dd, *J* = 13.9, 8.0 Hz, 1H), 1.51 (s, 9H), 1.26 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 176.8, 176.5, 173.9, 153.7, 135.6, 132.5, 132.1, 128.3, 127.9, 120.0, 81.8, 59.4, 59.0, 50.6, 49.7, 45.2, 41.0, 28.4, 22.4; **IR (Neat Film, NaCl)** 2976, 2932, 1698, 1426, 1367, 1286, 1246, 1136, 1027, 924, 858, 802, 750, 719, 695, 635 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{20}H_{27}N_2O_4$ $[M+H]^+$: 359.1965, found 359.1963; **$[\alpha]_D^{23.2}$** –25.7 (c 1.0, $CHCl_3$);

SFC conditions: 7% IPA, 2.5 mL/min, Chiralpak OJ-H column, λ = 254 nm, t_R (min): major = 3.209, minor = 2.569.

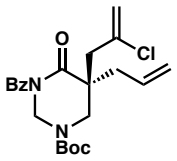


***tert*-butyl (*R*)-5-allyl-3-benzoyl-5-ethyl-4-oxotetrahydropyrimidine-1(2H)-carboxylate (6b).** Following the general procedure, ethylated allyl ester **5b** (15 mg, 0.036 mmol, 1.0 equiv) in hexanes/toluene (2:1, 1.0 mL) was added to a solution of $Pd_2(pmdba)_3$ (1.6 mg, 0.0014 mmol, 4 mol %) and (*S*)-$(CF_3)_3$-*t*Bu-PHOX (2.1 mg, 0.0036 mmol, 10 mol %) in hexanes/toluene (2:1, 1.6 mL). Purification by silica gel flash chromatography (13% EtOAc/hexanes) gave α-ethyl tetrahydropyrimidinone **6b** as a colorless oil (13 mg, 98% yield, 94% ee); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.57 – 7.45 (m, 3H), 7.39 (t, *J* = 7.5 Hz, 2H), 5.87 – 5.62 (m, 1H), 5.48 – 5.24 (m, 1H), 5.20 – 5.03 (m, 3H), 3.75 (dd, *J* = 14.0, 1.4 Hz, 1H), 3.65 – 3.52 (m, 1H), 2.50 (dd, *J* = 14.2, 6.7 Hz, 1H), 2.27 (d, *J* = 16.1 Hz, 1H), 1.79 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.68 (dq, *J* = 14.6, 7.4 Hz, 1H), 1.51 (s, 9H), 0.95 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 175.8, 174.1, 153.7, 135.8, 132.9, 132.0, 128.3, 128.0, 119.7, 81.7, 59.2, 58.8, 48.6, 48.0, 47.6, 39.1, 38.6, 28.7, 28.4, 8.4; **IR (Neat Film, NaCl)** 2976, 2927, 1698, 1426, 1367, 1286, 1263, 1246, 1136, 1017, 923, 859, 801, 738, 695, 635 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{21}H_{29}N_2O_4$ $[M+H]^+$: 373.2122, found: 373.2122; **$[\alpha]_D^{22.2}$** –21.0 (c 1.0, $CHCl_3$); **SFC conditions**: 7% IPA, 2.5 mL/min, Chiralpak OJ-H column, λ = 254 nm, t_R (min): major = 3.956, minor = 2.585.

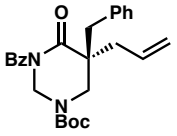


***tert*-butyl (*R*)-5-allyl-3-benzoyl-5-(3-methoxy-3-oxopropyl)-4-oxotetrahydropyrimidine-1(2H)-carboxylate (6c)**. Following the general procedure, methyl ester pyrimidinone **5c** (15 mg, 0.032 mmol, 1.0 equiv) in hexanes/toluene (2:1, 1.0 mL) was added to a solution of $Pd_2(pmdba)_3$ (1.2 mg, 0.0013 mmol, 4 mol %) and (*S*)-$(CF_3)_3$-*t*Bu-PHOX (1.9 mg, 0.0032 mmol, 10 mol %) in hexanes/toluene (2:1, 1.3 mL). Purification by silica gel flash chromatography (15% EtOAc/hexanes) gave methyl ester **6c** as a colorless oil (9.1 mg, 67% yield, 95% ee): **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.50 (dd, *J* = 13.1, 7.2 Hz, 3H), 7.38 (t, *J* = 7.5 Hz, 2H), 5.73 (dq, *J* = 16.6, 7.4 Hz, 1H), 5.47 – 5.22 (m, 1H), 5.22 – 5.04 (m, 3H), 3.66 (m, 5H), 2.49 (dt, *J* = 12.9, 6.4 Hz, 1H), 2.37 (m, 2H), 2.31 – 2.19 (m, 1H), 2.14 – 1.91 (m, 2H), 1.51 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 175.2, 174.9, 173.9, 173.3, 153.5, 135.6, 132.1, 132.0, 128.4, 127.9, 120.3, 82.0, 59.2, 58.8, 51.1, 48.7, 47.7, 39.1, 38.8, 30.3, 28.9, 28.3; **IR (Neat Film, NaCl)** 2978, 1738, 1698, 1428, 1368, 1286, 1247, 1147, 925, 856, 802, 764, 696 cm^{-1};

HRMS (MM: ESI-APCI): *m/z* calc'd for $C_{23}H_{31}N_2O_6$ $[M+H]^+$: 431.2177, found 431.2173; $[\alpha]_D^{23.1}$ +5.5 (c 0.9, $CHCl_3$); **SFC conditions**: 10% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): major = 5.591, minor = 6.372.

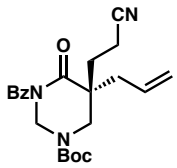


***tert*-butyl (*S*)-5-allyl-3-benzoyl-5-(2-chloroallyl)-4-oxotetrahydropyrimidine-1(2H)-carboxylate (6d)**. Following the general procedure, 2-chloropropenyl allyl ester **5d** (20 mg, 0.049 mmol, 1.0 equiv) in hexanes/toluene (2:1, 3.0 mL) was added to a solution of $Pd_2(pmdba)_3$ (2.1 mg, 0.0020 mmol, 4 mol %) and (*S*)-$(CF_3)_3$-*t*Bu-PHOX (2.9 mg, 0.0049 mmol, 10 mol %) in hexanes/toluene (2:1, 0.5 mL). Purification by flash chromatography (EtOAc/hexanes 15%) gave di-substituted oxopiperazine **6d** as a yellow oil (17 mg, 94% yield, 94% ee); **^{1}H NMR (400 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 7.65 – 7.45 (m, 3H), 7.40 (t, *J* = 7.6 Hz, 2H), 5.95 – 5.76 (m, 1H), 5.76 – 5.47 (m, 1H), 5.31 (d, *J* = 1.3 Hz, 1H), 5.30 – 5.16 (m, 2H), 4.92 (s, 1H), 4.05 (s, 1H), 3.61 (d, *J* = 14.0 Hz, 1H), 3.06 (d, *J* = 14.8 Hz, 1H), 2.69 – 2.55 (m, 1H), 2.45 (d, *J* = 14.5 Hz, 2H), 1.52 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 174.4, 173.9, 153.6, 137.5, 135.6, 132.1, 132.0, 128.3, 128.1, 120.8, 118.1, 82.0, 59.1, 48.2, 47.6, 46.6, 42.8, 42.3, 41.7, 28.4; **IR (Neat Film, NaCl)** 2977, 1698, 1630, 1478, 1426, 1368, 1286, 1246, 1140, 902, 802, 765, 724, 695, 636 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{22}H_{28}ClN_2O_4$ $[M+H]^+$: 419.1732, found 419.1732; $[\alpha]_D^{22.6}$ +22.2 (c 1.0, $CHCl_3$); **SFC conditions**: 10% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 4.679, minor = 3.777.

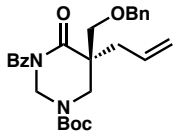


***tert*-butyl (*S*)-5-allyl-3-benzoyl-5-benzyl-4-oxotetrahydropyrimidine-1(2H)-carboxylate (6e).** Following the general procedure, benzylated allyl ester **5e** (15 mg, 0.031 mmol, 1.0 equiv) in hexanes/toluene (2:1, 1.0 mL) was added to a solution of $Pd_2(pmdba)_3$ (1.4 mg, 0.0013 mmol, 4 mol %) and (*S*)-$(CF_3)_3$-*t*Bu-PHOX (1.9 mg, 0.0031 mmol, 10 mol %) in hexanes/toluene (2:1, 1.2 mL). Purification by silica gel flash chromatography (13% EtOAc/hexanes) gave benzyl tetrahydropyrimidinone **6e** as a colorless oil (11.5 mg, 84% yield, 95% ee); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.58 – 7.49 (m, 3H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.31 – 7.24 (m, 3H), 7.20 (d, *J* = 7.2 Hz, 2H), 5.86 (dddd, *J* = 16.8, 10.2, 7.9, 6.6 Hz, 1H), 5.48 – 5.25 (m, 1H), 5.22 (d, *J* = 10.0 Hz, 1H), 5.21 – 5.14 (m, 1H), 4.87 (d, *J* = 11.9 Hz, 1H), 3.89 – 3.72 (m, 1H), 3.55 (d, *J* = 13.7 Hz, 1H), 3.37 – 3.21 (m, 1H), 2.80 – 2.68 (m, 1H), 2.65 (dd, *J* = 14.0, 6.6 Hz, 1H), 2.32 – 2.19 (m, 1H), 1.52 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 175.4, 173.9, 153.6, 136.1, 135.6, 132.6, 132.1, 131.0, 128.5, 128.3, 128.1, 127.1, 120.2, 81.9, 58.8, 49.5, 47.2, 46.5, 41.1, 40.6, 28.4**; IR (Neat Film, NaCl)** 2978, 2930, 2360, 1698, 1424, 1368, 1288, 1245, 1142, 1029,

924, 856, 802, 718, 696, 636 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{26}H_{31}N_2O_4$ $[M+H]^+$: 435.2278, found: 435.2274; **$[\alpha]_D^{22.1}$** –5.6 (c 1.0, $CHCl_3$); **SFC conditions**: 20% IPA, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, t_R (min): major = 4.096, minor = 4.670.

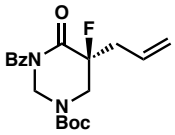


tert-butyl (R)-5-allyl-3-benzoyl-5-(2-cyanoethyl)-4-oxotetrahydropyrimidine-1(2H)-carboxylate (6f). Following the general procedure, cyanoethylated tetrahydropyrimidinone **5f** (15 mg, 0.034 mmol, 1.0 equiv) in hexanes/toluene (2:1, 1.0 mL) was added to a solution of $Pd_2(pmdba)_3$ (1.2 mg, 0.0014 mmol, 4 mol %) and (*S*)-$(CF_3)_3$-*t*Bu-PHOX (2.0 mg, 0.0034 mmol, 10 mol %) in hexanes/toluene (2:1, 1.4 mL). Purification by silica gel flash chromatography (20% EtOAc/hexanes) gave cyanoethylated tetrahydropyrimidinone **6f** as a colorless oil (9.0 mg, 67% yield, 74% ee): **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.56 – 7.49 (m, 3H), 7.43 (t, *J* = 7.6 Hz, 2H), 5.75 (dddd, *J* = 16.8, 10.2, 7.9, 6.6 Hz, 1H), 5.35 – 5.13 (m, 4H), 3.86 – 3.55 (m, 2H), 2.57 – 2.51 (m, 1H), 2.44 (dd, *J* = 10.0, 5.9 Hz, 2H), 2.32 (dd, *J* = 14.1, 8.0 Hz, 1H), 2.09 (dt, *J* = 14.6, 8.5 Hz, 1H), 1.96 (ddd, *J* = 14.3, 9.8, 6.2 Hz, 1H), 1.53 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.6, 173.7, 153.4, 135.4, 132.4, 131.2, 128.5, 127.8, 121.2, 119.2, 82.5, 59.4, 48.3, 47.7, 39.1, 31.0, 28.4, 12.6; **IR (Neat Film, NaCl)** 2977, 2931, 2248, 1694, 1601, 1478, 1427,1368, 1285, 1263, 1246, 1141, 1027, 926,901, 857, 802, 763, 721, 696, 636, cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{22}H_{28}N_3O_4$ $[M+H]^+$: 398.2074, found 398.2071; **$[\alpha]_D^{23.2}$** +10.0 (c 1.0, $CHCl_3$); **SFC conditions**: 30% IPA, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, t_R (min): major = 3.148, minor = 4.927.

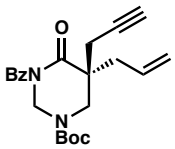


tert-butyl (*R*)-5-allyl-3-benzoyl-5-((benzyloxy)methyl)-4-oxotetrahydropyrimidine-1(2*H*)-carboxylate (6g). Following the general procedure, allyl ester **5g** (15 mg, 0.029 mmol, 1.0 equiv) in hexanes/toluene (2:1, 1.6 mL) was added to a solution of $Pd_2(pmdba)_3$ (1.3 mg, 0.0012 mmol, 4 mol %) and (*S*)-$(CF_3)_3$-*t*Bu-PHOX (1.7 mg, 0.0029 mmol, 10 mol %) in hexanes/toluene (2:1, 0.5 mL). Purification by flash chromatography (10 → 15% EtOAc/hexanes) gave di-substituted oxopiperazine **6g** as a yellow oil (13 mg, 87% yield, 87% ee): **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.69 – 7.51 (m, 2H), 7.51 – 7.42 (m, 1H), 7.42 – 7.22 (m, 7H), 5.77 (ddt, *J* = 15.0, 10.3, 7.4 Hz, 1H), 5.54 – 5.49 (m, 1H), 5.28 – 5.10 (m, 2H), 5.06 (d, *J* = 12.1 Hz, 1H), 4.63 – 4.40 (m, 2H), 3.94 (m, 1H), 3.82 (d, *J* = 13.9 Hz, 1H), 3.75 (d, *J* = 8.9 Hz, 1H), 3.40 (d, *J* = 9.0 Hz, 1H), 2.42 (m, 2H), 1.50 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.7, 173.5, 153.6, 137.8, 135.5, 132.0, 128.6, 128.3, 128.2,

127.9, 127.7, 112.0, 81.8, 73.8, 58.8, 50.0, 46.9, 46.3, 38.6, 28.4; **IR (Neat Film, NaCl)** 2977, 2926, 2283, 1698, 1641, 1478, 1451, 1426, 1367, 1287, 1246, 1151, 1028, 906, 857, 801, 740, 697, 635 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{27}H_{32}N_2O_5$ $[M+H]^+$: 465.2384, found 465.2378; **$[\alpha]_D^{23.4}$** +11.9 (c 0.67, $CHCl_3$); **SFC conditions:** 20% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): major = 5.131, minor = 4.419.



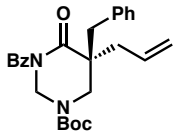
***tert*-butyl (*S*)-5-allyl-3-benzoyl-5-fluoro-4-oxotetrahydropyrimidine-1(2H)-carboxylate (6h)**. Following the general procedure, fluorinated tetrahydropyrimidinone **5h** (300 mg, 0.74 mmol, 1.0 equiv) in hexanes/toluene (2:1, 39 mL) was added to a solution of $Pd_2(pmdba)_3$ (24 mg, 0.022 mmol, 3 mol %) and (*S*)-$(CF_3)_3$-*t*Bu-PHOX (35 mg, 0.059 mmol, 10 mol %) in hexanes/toluene (2:1, 15 mL). Purification by silica gel flash chromatography (15% EtOAc/hexanes) gave fluorinated tetrahydropyrimidinone **6h** as a pale yellow oil (250 mg, 93% yield, 92% ee); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.59 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 5.82 (ddt, *J* = 14.9, 9.6, 7.2 Hz, 1H), 5.66 – 5.34 (m, 1H), 5.29 (s, 1H), 5.25 (d, *J* = 5.3 Hz, 1H), 5.24 – 5.13 (m, 1H), 4.13 – 3.72 (m, 2H), 2.81 (td, *J* = 14.3, 6.9 Hz, 1H), 2.67 (ddd, *J* = 22.4, 14.5, 7.6 Hz, 1H), 1.51 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 172.5, 168.23 (d, J_{CF} = 23.6 Hz), 153.4, 134.3, 132.7, 129.7, 129.6, 128.5, 128.5, 128.3, 128.0, 121.4, 92.2 (d, J_{CF} = 197.0 Hz, appears as four peaks due to the presence of two rotamers and coupling with fluorine), 82.4, 57.7, 49.4 (appears as four poorly resolved peaks due to the presence of two rotamers and coupling with fluorine), 38.2 (d, J_{CF} = 22.8 Hz), 28.3; **IR (Neat Film, NaCl)** 2978, 1710, 1416, 1368, 1286, 1245, 1158, 1137, 906, 858, 801, 749, 723, 694, 662 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{19}H_{24}N_2O_4$ $[M+H]^+$: 363.1715, found: 363.1713; **$[\alpha]_D^{21.8}$** –28.6 (c 0.96, $CHCl_3$); **SFC conditions**: 10% IPA, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, t_R (min): major = 6.226, minor = 5.041.



***tert*-butyl (*S*)-5-allyl-3-benzoyl-4-oxo-5-(prop-2-yn-1-yl)tetrahydropyrimidine-1(2H)-carboxylate (6i)**. Following the general procedure, propargylated allyl ester **5i** (20 mg, 0.047 mmol, 1.0 equiv) in hexanes/toluene (2:1, 2.8 mL) was added to a solution of $Pd_2(pmdba)_3$ (2.1 mg, 0.0019 mmol, 4 mol %) and (*S*)-$(CF_3)_3$-*t*Bu-PHOX (2.8 mg, 0.0047 mmol, 10 mol %) in hexanes/toluene (2:1, 0.5 mL). Purification by flash chromatography (EtOAc/hexanes 5% → 10% → 15%) gave propargyl tetrahydropyrimidinone **6i** as a yellow oil (15 mg, 83% yield, 90% ee): **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.58 (s, 1H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 5.89 – 5.68 (m, 1H), 5.42 (s, 1H), 5.31 – 4.98 (m, 3H), 4.15 – 3.57 (m, 2H), 2.61 (dd, *J* = 16.9, 2.7 Hz, 2H), 2.42 (dd, *J* = 16.9, 2.7 Hz,

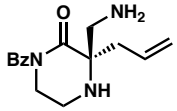
2H), 2.11 (t, *J* = 2.6 Hz, 1H), 1.54 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ (a mixture of two rotamers) 174.3, 173.7, 153.6, 135.4, 132.2, 131.8, 128.3, 128.2, 120.6, 82.0, 79.6, 72.4, 59.3, 58.9, 48.2, 47.8, 40.1, 39.6, 28.4, 25.1; **IR (Neat Film, NaCl)** 3271, 2978, 2930, 1698, 1478, 1450, 1425, 1368, 1284, 1247, 1139, 1028, 927, 854, 802, 764, 720, 695, 635 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{22}H_{27}N_2O_4$ $[M+H]^+$: 383.1965, found 383.1973; **$[\alpha]_D^{23.0}$** +22.1 (c 0.47, $CHCl_3$); **SFC conditions:** 10% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 4.769, minor = 4.399.

Experimental Procedure for the Gram Scale Decarboxylative Asymmetric Allylic Alkylation of Benzyl Tetrahydropyrimidinone 5e



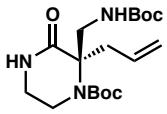
***tert*-butyl (*S*)-5-allyl-3-benzoyl-5-benzyl-4-oxotetrahydropyrimidine-1(2H)-carboxylate (6e).** In a nitrogen-filled glovebox, a 250 mL schlenk flask was charged with $Pd_2(pmdba)_3$ (69 mg, 0.063 mmol, 4 mol %), (*S*)-$(CF_3)_3$-*t*Bu-PHOX (99 mg, 0.17 mmol, 8 mol %), hexane/toluene (2:1, 50 mL), and a magnetic stir bar. The flask was stirred at ambient glovebox temperature (27 °C) for 30 min and then **5e** (1g, 2.1 mmol, 1.0 equiv) was added as a solution in hexane/toluene (2:1, 100 mL, total concentration 0.014M). The flask was sealed with a Kontes valve, removed from the glovebox, and heated to 40 °C for 16 h. The solution was concentrated under reduced pressure and purified by silica gel flash chromatography (15% EtOAc/hexanes) to give benzyl tetrahydropyrimidinone **6e** as a yellow oil (780 mg, 87% yield, 95% ee); spectroscopic data vide supra.

Experimental Procedures for the Transformations of Decarboxylative Allylic Alkylation Products

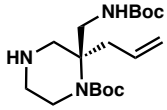


***tert*-butyl (*R*)-((2-allyl-4-benzoyl-3-oxopiperazin-2-yl)methyl)carbamate (8)**. Trifluoroacetic acid (114 μL, 1.5 mmol, 20 equiv) was added dropwise to a solution of methylcarbamate oxopiperazine **4m** (35 mg, 0.07 mmol, 1.0 equiv) in CH_2Cl_2 (0.74 mL) at 0 °C. The reaction mixture was allowed to warm up to room temperature, stirred for 3 h and concentrated under reduced pressure. The residue was repeatedly taken up in CH_2Cl_2 (1.0 mL) and concentrated, four times. The crude residue was then purified by silica gel flash chromatography (10% MeOH/CH_2Cl_2) to yield deprotected oxopiperazine **8** as a pale yellow foam (27 mg, 73% yield); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.48 (t, *J* = 8.0 Hz, 3H), 7.37 (t, *J* = 7.4 Hz, 2H), 5.66 (dd, *J* = 16.0, 8.8 Hz, 1H), 5.30 (d, *J* = 9.8 Hz, 1H), 5.25 (d, *J* = 16.8 Hz, 1H), 3.99 – 3.79 (m, 1H), 3.73 –

3.55 (m, 1H), 3.44 – 3.16 (m, 2H), 3.05 (d, J = 13.2 Hz, 1H), 2.89 (d, J = 11.6 Hz, 1H), 2.76 (dd, J = 14.0, 7.0 Hz, 1H), 2.45 (dd, J = 14.2, 7.1 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.7, 172.4, 135.5, 132.2, 129.7, 128.4, 128.0, 122.5, 62.0, 47.0, 43.5, 39.7, 38.1; **IR (Neat Film, NaCl)** 2976, 1682, 1470, 1282, 1203, 1135, 926, 836, 799, 722, 696 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{15}H_{20}N_3O_4$ $[M+H]^+$: 274.1550, found 274.1555; **$[\alpha]_D^{22.3}$** +15.1 (c 1.0, $CHCl_3$).

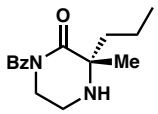


***tert*-butyl (*R*)-2-allyl-2-(((*tert*-butoxycarbonyl)amino)methyl)-3-oxopiperazine-1-carboxylate** (**9**). LiOH monohydrate (2.5 mg, 0.06 mmol, 1.4 equiv) was added in one portion to a solution of methylcarbamate oxopiperazine **4m** (20 mg, 0.04 mmol, 1.0 equiv) in methanol/water (1:1, 1.8 mL) at room temperature. The reaction mixture was stirred for 1 h, diluted with EtOAc (2 mL) and washed with saturated aqueous $NaHCO_3$ (2 mL). The aqueous phase was extracted with EtOAc (3x3 mL) and the combined organic phases were washed with brine (3 mL), dried over anhydrous Na_2SO_4, decanted, and concentrated under reduced pressure onto silica gel. The silica-loaded residue was purified by silica gel flash chromatography (hexanes/EtOAc 1:1) to yield lactam **9** as a white foam (14 mg, 92% yield): **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.96 (s, 1H), 5.72 (ddt, J = 17.2, 10.2, 7.4 Hz, 1H), 5.16 – 5.04 (m, 2H), 4.88 (t, J = 6.9 Hz, 1H), 4.26 – 3.91 (m, 1H), 3.82 (s, 1H), 3.60 (dd, J = 14.0, 5.9 Hz, 1H), 3.50 (s, 1H), 3.39 – 2.83 (m, 3H), 2.62 (s, 1H), 1.52 (s, 9H), 1.41 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.7, 155.7, 153.9, 132.7, 119.2, 81.2, 79.3, 69.1, 46.0, 43.1, 40.9, 38.9, 28.6, 28.5; **IR (Neat Film, NaCl)** 3337, 2977, 2360, 1698, 1520, 1367, 1243, 1168, 1085, 1058, 919, 866, 768, 733 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{18}H_{32}N_3O_5$ $[M+H]^+$: 370.2336, found 370.2337; **$[\alpha]_D^{21.9}$** –5.7 (c 1.0, $CHCl_3$).

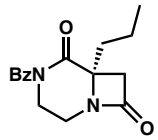


***tert*-butyl (*S*)-2-allyl-2-(((tert-butoxycarbonyl)amino)methyl)piperazine-1-carboxylate** (**10**). To a solution of lactam **9** (50 mg, 0.14 mmol, 1 equiv) in THF (1.4 mL) at 0 °C was quickly added LAH (8 mg, 0.2 mmol, 1.5 equiv) in one portion. The mixture was stirred at room temperature and three portions of LAH (8 mg, 0.2 mmol, 1.5 equiv) were added over four hours until all starting material was consumed as determined by TLC analysis. The reaction mixture was then cooled to 0 °C and diluted with Et_2O. H_2O (40 μL), 15% aqueous NaOH (40 μL), and H_2O (120 μL) were added successively at 0 °C. The mixture was stirred for 5 minutes at room temperature and then $MgSO_4$ was added. The mixture was stirred for another 5 minutes at room temperature and then filtered over a pad of celite, rinsing with EtOAc. The solvent was concentrated under reduced pressure and the crude residue was purified by silica gel flash chromatography ($MeOH/CH_2Cl_2$, 1 → 2 → 4%) to afford piperazine **10** as a colorless oil (30 mg, 63% yield); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.84 – 5.66 (m, 1H), 5.28 – 5.01 (m, 3H), 3.75 (dd, J = 14.1, 5.6 Hz, 1H), 3.62 (dt, J = 13.6, 4.2 Hz, 1H), 3.35 (dd, J = 14.1, 7.3 Hz, 1H), 3.24 (ddd, J = 13.6, 9.8, 3.8 Hz,

1H), 3.02 – 2.91 (m, 1H), 2.85 (t, *J* = 11.1 Hz, 2H), 2.79 – 2.63 (m, 2H), 2.57 – 2.26 (m, 2H), 1.46 (s, 9H), 1.44 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 156.8, 156.0, 133.1, 119.1, 80.6, 79.6, 59.9, 50.8, 46.2, 45.1, 42.3, 38.1, 28.6, 28.5; **IR (Neat Film, NaCl)** 3789, 3662, 3451, 3341, 3074, 2976, 2930, 2284, 1693, 1641, 1502, 1453, 1391, 1365, 1298, 1249, 1169, 1085, 996, 914, 859, 771 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{18}H_{34}N_3O_4$ $[M+H]^+$: 356.2544, found 356.2549; **$[\alpha]_D^{22.8}$** +5.3 (c 0.67, $CHCl_3$).

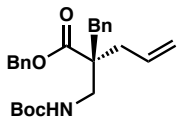


(*S*)-1-benzoyl-3-methyl-3-propylpiperazin-2-one 11. Piperazinone **4e** (80 mg, 0.22 mmol, 1 equiv) was dissolved in MeOH (2.2 mL). The reaction flask was purged with Argon before adding Pd/C (10%, 24 mg, 0.022 mmol, 0.1 equiv). The flask was evacuated and filled with H_2 three times, and then sparged with H_2 for 5 minutes. The reaction was stirred at room temperature for 6 hours before being filtered through a pad of silica gel while rinsing with EtOAc. The crude hydrogenated product was then dissolved in CH_2Cl_2 (2.2 mL) and TFA (171 μL, 2.23 mmol, 10 equiv) was added. The reaction was stirred for 16 hours and then quenched with saturated aqueous $NaHCO_3$ (5 mL). The solution was extracted with EtOAc (3x5 mL), dried over Na_2SO_4, decanted, and concentrated under reduced pressure. The crude piperazinone was purified by silica gel flash chromatography (2.5 → 5% MeOH/CH_2Cl_2) to afford the desired product **11** (55 mg, 94% yield over two steps): **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.58 – 7.50 (m, 2H), 7.54 – 7.46 (m, 1H), 7.46 – 7.36 (m, 2H), 3.92 (ddd, *J* = 12.6, 5.4, 4.6 Hz, 1H), 3.81 (ddd, *J* = 12.5, 6.7, 5.4 Hz, 1H), 3.32 – 3.18 (m, 2H), 1.92 (ddd, *J* = 13.6, 12.1, 4.7 Hz, 1H), 1.62 (ddd, *J* = 13.6, 12.2, 4.5 Hz, 1H), 1.42 (s, 3H), 1.54 – 1.23 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 176.7, 174.7, 136.4, 131.6, 128.3, 127.5, 61.2, 48.2, 41.2, 38.7, 25.0, 16.9, 14.5; **IR (Neat Film, NaCl)** 3331, 2960, 2872, 1681, 1600, 1448, 1378, 1284, 1202, 1176, 1152, 1112, 966, 794, 726, 694, 669 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{15}H_{21}N_2O_2$ $[M+H]^+$: 261.1598, found 261.1596; **$[\alpha]_D^{22.6}$** –59.6 (c 1.35, $CHCl_3$).



(*R*)-4-benzoyl-6-propyl-1,4-diazabicyclo[4.2.0]octane-5,8-dione (12). To a 10 mL round-bottom flask was added $Pd(OPiv)_2$ (3 mg, 0.0096 mmol, 0.1 equiv), AgOPiv[7] (60 mg, 0.29 mmol, 3 equiv), Xantphos (6 mg, 0.0096 mmol, 0.1 equiv), and 1,4-benzoquinone (21 mg, 0.19 mmol, 2 equiv). A solution of piperazine **11** (25 mg, 0.096 mmol, 1 equiv) in toluene (1 mL) was then added and the flask was evacuated and filled with carbon monoxide three times. The flask was then stirred at 80 °C for 16 hours. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc, and filtered through celite while rinsing with additional EtOAc. The solvent was concentrated under reduced

pressure onto silica gel and then purified by silica gel flash chromatography (2:1 hexanes/EtOAc) to provide the *β*-lactam **12** and as a light yellow oil (15 mg, 55% yield): **^{1}H NMR (400 MHz, $CDCl_3$)** δ (5:1 ratio of desired product and an inseparable isomer resulting from insertion into another *β*-C−H) 7.56 – 7.51 (m, 3H), 7.46 – 7.40 (m, 2H), 4.51 (ddd, *J* = 14.0, 6.1, 2.9 Hz, 1H), 3.94 (ddt, *J* = 12.3, 10.8, 5.7 Hz, 1H), 3.78 – 3.67 (m, 1H), 3.40 (dddd, *J* = 12.3, 4.8, 2.8, 1.5 Hz, 1H), 3.27 – 3.10 (m, 2H), 1.98 (ddd, *J* = 14.2, 11.2, 5.5 Hz, 1H), 1.87 (ddd, *J* = 14.2, 11.0, 5.7 Hz, 1H), 1.59 – 1.40 (m, 2H), 1.00 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.2, 173.2, 169.1, 135.1, 132.6, 128.6, 128.3, 59.7, 46.7, 41.5, 39.7, 37.8, 17.7, 14.3; **IR (Neat Film, NaCl)** 3374, 2961, 1760, 1688, 1600, 1505, 1449, 1350, 1318, 1279, 1228, 1183, 1151, 1110, 963, 936, 796, 726, 694, 662 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{16}H_{19}N_2O_3$ $[M+H]^+$: 287.1390, found 287.1385; **$[\alpha]_D^{23.5}$** –12.8 (c 0.47, $CHCl_3$).

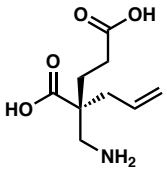


(*S*)-2-benzyl-2-(((tert-butoxycarbonyl)amino)methyl)pent-4-enoic acid (13). To a solution of benzyl tetrahydropyrimidinone **6e** (200 mg, 0.46 mmol, 1 equiv) in methylene chloride (4.6 mL) was added TFA (352 μL, 4.6 mmol, 10 equiv) dropwise at room temperature. The solution was stirred for 24 hours at room temperature and then quenched with aqueous $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

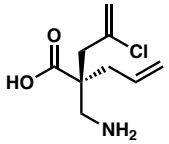
The crude residue was dissolved in MeOH/H_2O (1:1, 5 mL) and LiOH monohydrate (290 mg, 6.9 mmol, 15 equiv) was added. The reaction mixture was heated to 80 °C for 60 hours and then allowed to cool to room temperature. Then, NEt_3 (77 μL, 0.55 mmol, 1.2 equiv) and Boc_2O (110 mg, 0.51 mmol, 1.1 equiv) were added successively at room temperature. The reaction was stirred for 1 hour at room temperature and then acidified with 1 M HCl (4 mL). The solution was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_4.

The crude Boc-protected *β*-amino acid was taken up in DMF (2.3 mL). K_2CO_3 (95 mg, 0.69 mmol, 1.5 equiv) and BnBr (66 μL, 0.55 mmol, 1.2 equiv) were added at room temperature. The reaction was stirred at room temperature for 1 hour and then quenched with saturated aqueous NH_4Cl. The solution was extracted with EtOAc (3 x 5 mL) and the combined organic layers were concentrated under reduced pressure and placed under high vacuum until trace DMF had evaporated. The residue was taken up in CH_2Cl_2, concentrated under reduced pressure onto silica gel and purified by silica gel flash chromatography (5 → 10% EtOAc/hexanes) to afford protected $\beta^{2,2}$-amino acid **13** as a white solid (80 mg, 40% yield): **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.42 – 7.27 (m, 5H), 7.20 (dd, *J* = 4.9, 1.9 Hz, 3H), 7.10 – 6.93 (m, 2H), 5.92 – 5.75 (m, 1H), 5.18 – 5.04 (m, 4H), 4.96 – 4.81 (m, 1H), 3.34 (qd, *J* = 14.0, 6.5 Hz, 2H), 2.98 (d, *J* = 13.8 Hz, 1H), 2.86 (d, *J* = 13.8 Hz, 1H), 2.49 (ddt, *J* = 14.2, 6.7, 1.4 Hz, 1H), 2.31 (ddt, *J* = 14.2, 7.9, 1.1 Hz, 1H), 1.43 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 175.1, 156.1, 136.6, 135.6, 133.4, 130.2, 128.8, 128.6, 128.5, 128.4, 126.9, 119.2, 79.4, 66.8, 51.6, 44.1, 41.0, 38.8, 28.5; **IR (Neat Film, NaCl)** 3452,

3065, 3031, 2977, 2930, 1721, 1640, 1604, 1503, 1454, 1391, 1365, 1245, 1169, 1094, 1030z, 994, 917, 859, 776, 741, 700 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_{25}H_{32}NO_4$ $[M+H]^+$: 410.2326, found 410.2324; $[\alpha]_D^{23.4}$ +3.47 (c 1.0, $CHCl_3$).

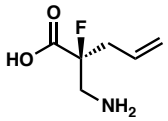


(*R*)-2-allyl-2-(aminomethyl)pentanedioic acid (**14**). To a solution of methyl ester tetrahydropyrimidinone **6c** (140 mg, 0.325 mmol, 1 equiv) in CH_2Cl_2 (3.1 mL, 0.1 M) was added TFA (250 µL, 3.25 mmol, 10 equiv) dropwise at room temperature. The solution was stirred for 24 h at room temperature and then concentrated under reduced pressure. Remaining TFA was removed with by azeotroping with CH_2Cl_2 three times. The crude residue was dissolved in MeOH/H_2O (1:1, 3.1 mL, 0.1 M) and LiOH monohydrate (205 mg, 4.89 mmol, 15 equiv) was added. The reaction mixture was heated to 80 °C for 16 h and then allowed to cool to room temperature. The reaction mixture was then acidified with 4 M HCl in dioxanes (~1 mL) until pH 1. Then, the solvent was concentrated under reduced pressure, resulting in precipitation of a white solid. A minimal amount of DMSO (~1 mL) was added to resolvate this precipitate. This solution was subjected to purification by reverse phase preparatory HPLC (0 → 40% MeCN/H_2O gradient over 11 minutes, 20x250 mm C_{18} column, 25 mL/min flow rate) to yield *β*-amino acid **14** (30 mg, 46% yield) as a colorless oil. Note: HPLC fractions were spotted onto a silica TLC plate and eluted in (*n*-BuOH/H_2O/EtOAc/AcOH, 1:1:1:1), then stained with ninhydrin to identify product-containing fractions. LC-MS was used to verify the fractions containing product. Note: HPLC H_2O solvent contained 0.25% TFA. **^{1}H NMR (400 MHz, Methanol-*d*$_4$)** δ 5.88 – 5.68 (m, 1H), 5.32 – 5.13 (m, 2H), 3.18 – 2.99 (m, 2H), 2.51 (ddt, *J* = 14.4, 7.1, 1.3 Hz, 1H), 2.47 – 2.33 (m, 3H), 1.99 (td, *J* = 7.6, 1.3 Hz, 2H); **^{13}C NMR (101 MHz, MeOD)** δ 176.7, 176.6, 133.1, 120.6, 48.3, 43.5, 39.1, 29.38, 29.35; **IR (Neat Film, NaCl)** 2924, 1678, 1198, 1138 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_9H_{16}NO_4$ $[M+H]^+$: 202.1074, found 202.1075; $[\alpha]_D^{22.7}$ –3.51 (c 1.0, MeOH).



(*S*)-2-allyl-2-(aminomethyl)-4-chloropent-4-enoic acid (**15**). To a solution of chloroallyl tetrahydropyrimidinone **6d** (30 mg, 0.072 mmol, 1 equiv) in CH_2Cl_2 (700 µL, 0.1 M) was added TFA (55 µL, 0.72 mmol, 10 equiv) dropwise at room temperature. The solution was stirred for 5 h at room temperature and then concentrated under reduced pressure. Remaining TFA was removed with by azeotroping with CH_2Cl_2 three times. The crude residue was dissolved in MeOH/H_2O (1:1, 700 µL, 0.1 M) and LiOH monohydrate (45 mg, 1.07 mmol, 15 equiv) was added. The reaction mixture was heated to 80 °C for 16 h and then allowed to cool to room temperature. The reaction mixture was then acidified with 4 M HCl in dioxane (~1 mL) until pH 1. Then, the solvent was concentrated under reduced pressure, resulting in precipitation of a white solid. A minimal amount of DMSO (~1 mL) was added to resolvate this precipitate. This solution was subjected to purification by

reverse phase preparatory HPLC (10 → 40% MeCN/H_2O gradient over 11 minutes, 20x250 mm C_{18} column, 25 mL/min flow rate) to yield chloroallyl *β*-amino acid **15** (10 mg, 69% yield) as a colorless oil. Note: HPLC fractions were spotted onto a silica TLC plate and eluted in (*n*-BuOH/H_2O/EtOAc/AcOH, 1:1:1:1), then stained with ninhydrin to identify product-containing fractions. LC-MS was used to verify the fractions containing product. Note: HPLC H_2O solvent contained 0.25% TFA. **^{1}H NMR (600 MHz, Methanol-*d*$_4$)** δ 5.84 (td, *J* = 17.2, 7.3 Hz, 1H), 5.40 (s, 2H), 5.28 – 5.18 (m, 2H), 3.29 (d, *J* = 13.5 Hz, 1H), 3.12 (d, *J* = 13.5 Hz, 1H), 2.94 (d, *J* = 15.1 Hz, 1H), 2.77 (d, *J* = 14.8 Hz, 1H), 2.57 (dd, *J* = 14.5, 7.0 Hz, 1H), 2.47 (dd, *J* = 14.5, 7.8 Hz, 1H); **^{13}C NMR (101 MHz, MeOD)** δ 176.6, 138.2, 133.1, 120.8, 118.7, 48.4, 44.2, 43.5, 39.6. Note: A ^{1}H-^{13}C HMBC experiment revealed the chemical shift of the chiral quaternary carbon to be at 48.4 ppm, obscured by the CD_3OD resonance. **IR (Neat Film, NaCl)** 2926, 1673, 1432, 1200, 1140, 900, 836, 800, 722 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_9H_{15}ClNO_2$ $[M+H]^+$: 204.0786, found 204.0787; **$[\alpha]_D^{22.5}$** –4.64 (c 0.67, MeOH).

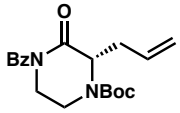
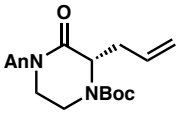
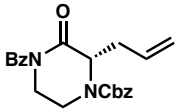
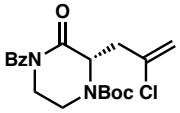
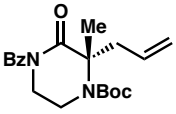
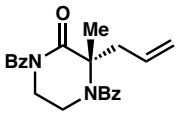
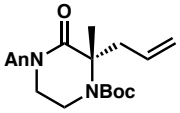
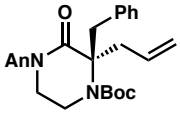


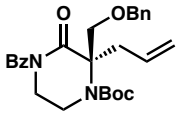
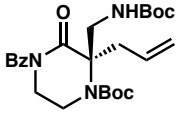
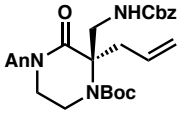
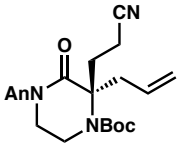
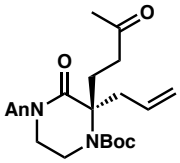
(*S*)-2-(aminomethyl)-2-fluoropent-4-enoic acid (16). To a solution of fluoro tetrahydropyrimidinone **6h** (20 mg, 0.055 mmol, 1 equiv) in 1:1 MeOH/H_2O (550 µL, 0.1 M) at room temperature was added KOH (31 mg, 0.55 mmol, 10 equiv). The cloudy solution became clear over seconds and was stirred for 5 min at room temperature until TLC analysis showed complete consumption of starting material. AcOH (~100 µL) was added to acidify the solution, which was then extracted with CH_2Cl_2 three times. The combined organic layers were dried with Na_2SO_4 and then concentrated under reduced pressure.

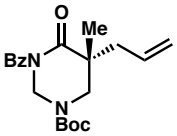
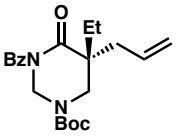
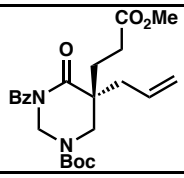
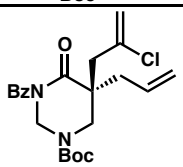
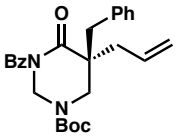
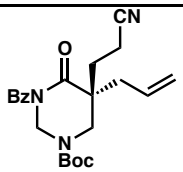
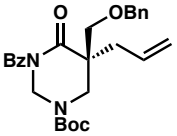
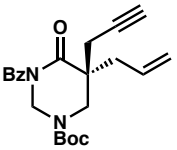
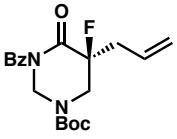
HCl was generated *in situ* by adding AcCl (205 µL, 2.87 mmol, 52 equiv) dropwise to a separate 1 dram vial containing MeOH (550 µL) at 0 °C. This HCl solution was stirred for 5 min at 0 °C and was then transferred by pipette into a 1 dram vial containing the crude saponified residue. The reaction was stirred at rt for 2 h and was then concentrated under reduced pressure. The crude residue was dissolved in 1:1 H_2O/MeCN (2.5 mL) and was then subjected to purification by reverse phase preparatory HPLC (0 → 40% MeCN/H_2O gradient over 11 minutes, 20x250 mm C_{18} column, 25 mL/min flow rate) to yield fluoro *β*-amino acid **16** (5.0 mg, 65% yield) as a colorless oil. Note: HPLC fractions were spotted onto a silica TLC plate and eluted in (*n*-BuOH/H_2O/EtOAc/AcOH, 1:1:1:1), then stained with ninhydrin to identify product-containing fractions. LC-MS was used to verify the fractions containing product. Note: HPLC H_2O solvent contained 0.25% TFA. **^{1}H NMR (600 MHz, Methanol-*d*$_4$)** δ 5.80 (ddt, *J* = 17.3, 10.1, 7.2 Hz, 1H), 5.30 – 5.17 (m, 2H), 3.51 (dd, *J* = 26.1, 13.9 Hz, 1H), 3.38 – 3.32 (dd, *J* = 26.1, 13.9 Hz, 1H), 2.81 – 2.63 (m, 2H); **^{13}C NMR (101 MHz, MeOD)** δ 171.1 (d, J_{CF} = 26.2 Hz), 130.7, 121.3, 95.0 (d, J_{CF} = 190.2 Hz), 44.74 (d, J_{CF} = 22.1 Hz), 40.44 (d, J_{CF} = 22.1 Hz); **IR (Neat Film, NaCl)** 2924, 1674, 1422, 1202, 1141, 931, 798, 722 cm^{-1}; **HRMS (MM: ESI-APCI):** *m/z* calc'd for $C_6H_{11}NO_2$ $[M+H]^+$: 148.0768, found 148.0770; **$[\alpha]_D^{22.5}$** –2.47 (c 0.33, MeOH).

Determination of Enantiomeric Excess

Please note racemic products were synthesized according to the general procedure, using achiral GlyPHOX ligand instead of (*S*)-$(CF_3)_3$-*t*Bu-PHOX.[3]

Entry	Product	Assay Conditions	Retention time of major isomer (min)	Retention time of minor isomer (min)	%ee
1		SFC Chiralpak AD-H 15% *i*PrOH isocratic, 2.5 mL/min	3.741	2.682	92%
2		SFC Chiralpak AD-H 15% *i*PrOH isocratic, 2.5 mL/min	4.708	3.998	96%
3		SFC Chiralpak IC 30% *i*PrOH isocratic, 2.5 mL/min	4.873	6.748	99%
4		SFC Chiralpak AD-H 15% *i*PrOH isocratic, 2.5 mL/min	4.482	3.224	98%
5		SFC Chiralpak AD-H 7% *i*PrOH isocratic, 2.5 mL/min	7.208	4.714	96%
6		SFC Chiralpak OJ-H 10% MeOH isocratic, 2.5 mL/min	5.574	6.659	70%
7		SFC Chiralpak AD-H 10% *i*PrOH isocratic, 2.5 mL/min	5.370	4.278	96%
8		SFC Chiralpak AD-H 15% *i*PrOH isocratic, 2.5 mL/min	7.471	5.802	96%

Entry	Product	Assay Conditions	Retention time of major isomer (min)	Retention time of minor isomer (min)	%ee
9		SFC Chiralpak OJ-H 7% *i*PrOH isocratic, 2.5 mL/min	3.737	4.398	92%
10		SFC Chiralpak OD-H 10% *i*PrOH isocratic, 2.5 mL/min	4.429	3.910	93%
11		SFC Chiralpak OD-H 15% MeOH isocratic, 2.5 mL/min	8.425	7.817	92%
12		SFC Chiralpak OD-H 15% *i*PrOH isocratic, 2.5 mL/min	6.049	5.143	97%
13		SFC Chiralpak OD-H 7% *i*PrOH isocratic, 2.5 mL/min	9.712	10.434	97%

Entry	Product	Assay Conditions	Retention time of major isomer (min)	Retention time of minor isomer (min)	%ee
14		SFC Chiralpak OJ-H 7% *i*PrOH isocratic, 2.5 mL/min	3.209	2.569	93%
15		SFC Chiralpak OJ-H 7% *i*PrOH isocratic, 2.5 mL/min	3.956	2.585	94%
16		SFC Chiralpak AD-H 10% *i*PrOH isocratic, 2.5 mL/min	5.591	6.372	95%
17		SFC Chiralpak AD-H 10% *i*PrOH isocratic, 2.5 mL/min	4.679	3.777	94%
18		SFC Chiralpak IC 20% iPrOH isocratic, 2.5 mL/min	4.096	4.670	95%
19		SFC Chiralpak IC 30% *i*PrOH isocratic, 2.5 mL/min	3.148	4.927	74%
20		SFC Chiralpak IC 20% *i*PrOH isocratic, 2.5 mL/min	5.131	4.419	87%
21		SFC Chiralpak AD-H 10% *i*PrOH isocratic, 2.5 mL/min	4.769	4.399	90%
22		SFC Chiralpak IC 10% *i*PrOH isocratic, 2.5 mL/min	6.226	5.041	92%

References

(1) a) D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045; b) J. T. Mohr, D. C. Behenna, A. M. Harned, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2005**, *44*, 6924–6927; *Angew. Chem.* **2005**, *117*, 7084–7087; c) M. Seto, J. L. Roizen, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2008**, *47*, 6873–6876; *Angew. Chem.* **2008**, *120*, 6979–6982; d) J. Streuff, D. E. White, S. C. Virgil, B. M. Stoltz, *Nat. Chem.* **2010**, *2*, 192–196; e) D. C. Behenna, Y. Liu, T. Yurino, J. Kim, D. E. White, S. C. Virgil, B. M. Stoltz, *Nat. Chem.* **2012**, *4*, 130–133; f) C. M. Reeves, C. Eidamshaus, J. Kim, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2013**, *52*, 6718–6721; *Angew. Chem.* **2013**, *125*, 6850–6853.

(2) M. E. Childs, W . P. Weber, *J. Org. Chem.* **1976**, *41*, 3486–3487.

(3) (a) D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045. (b) K. Tani, D. C. Behenna, R. M. McFadden, B. M. Stoltz, *Org. Lett.* **2007**, *9*, 2529– 2531. (c) M. R. Krout, J. T. Mohr, B. M. Stoltz, *Org. Synth.* **2009**, *86*, 181–193.

(4) K. M. Korch, C. Eidamshaus, D. C. Behenna, S. Nam, D. Horne, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2015**, *54*, 179–183.

(5) T. Ukai, H. Kawazura, Y. Ishii, J. J. Bonnet, J. A. Ibers, *J. Organomet. Chem.* **1999**, *65*, 253–266.

(6) I. J. S. Fairlamb, A. R. Kapdi, A. F. Lee, *Org. Lett.* **2004**, *6*, 4435–4438.

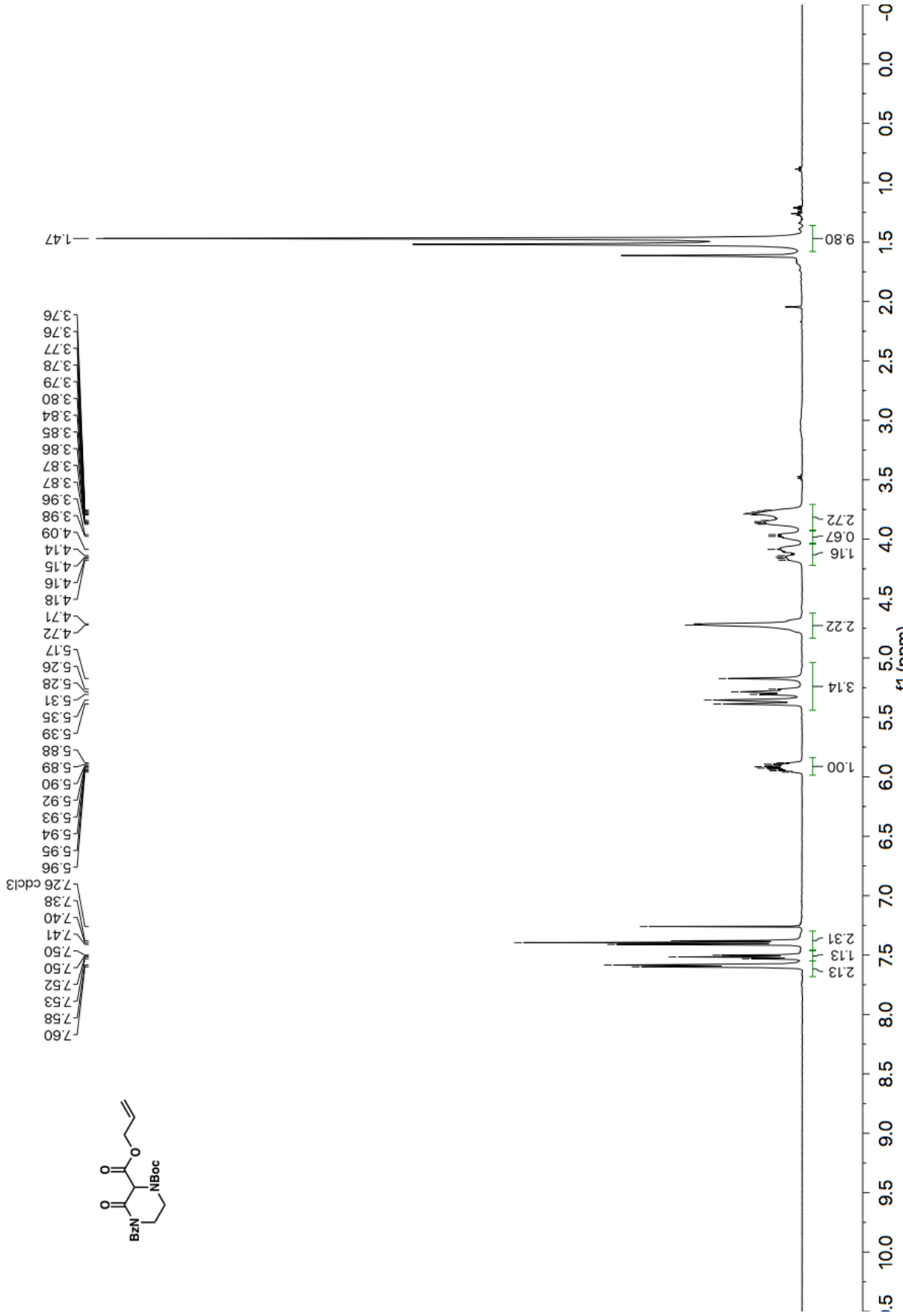
(7) K. Endo, R. H. Grubbs, *J. Am. Chem. Soc.* **2011**, *133*, 8525–8527.

(8) (a) Klepacz, A.; Zwierzak, A. *Tetrahedron Lett.* **2002**, *43*, 1079. (b) Sikriwal, D.; Kant, R.; Maulik, P. R.; Dikshit, D. K. *Tetrahedron* **2010**, *66*, 6167.

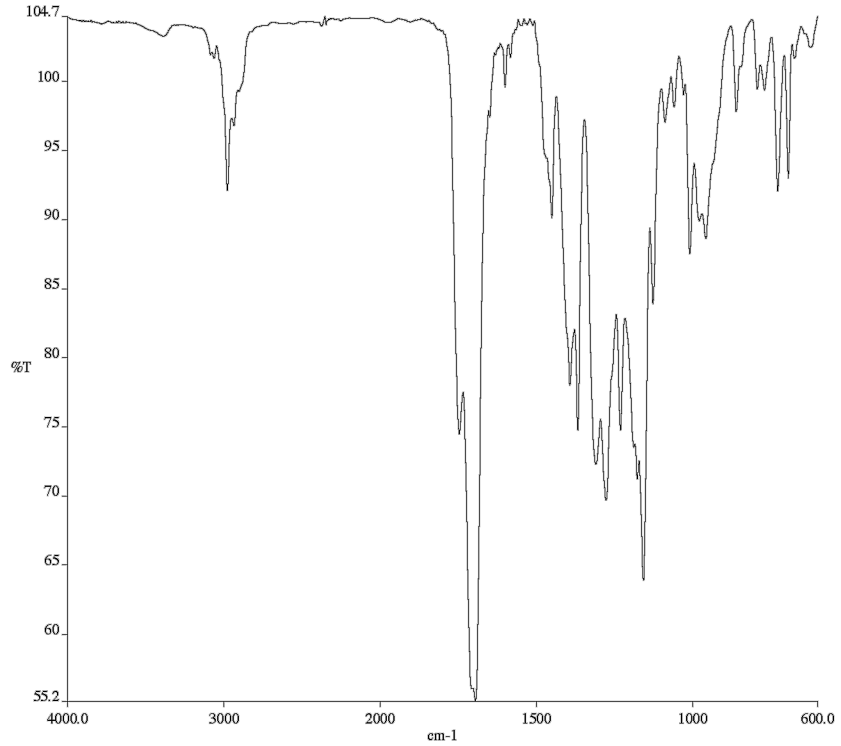
(9) R. R. R. Taylor, H. C. Twin, W. W. Wen, R. J. Mallot, A. J. Lough, S. D. Gray-Owen, R. A. Batey, *Tetrahedron* **2010**, *66*, 3370–3377.

(10) D. E. White, I. C. Stewart, R. H. Grubbs, B. M. Stoltz, *J. Am. Chem. Soc.* **2008**, *130*, 810–811.

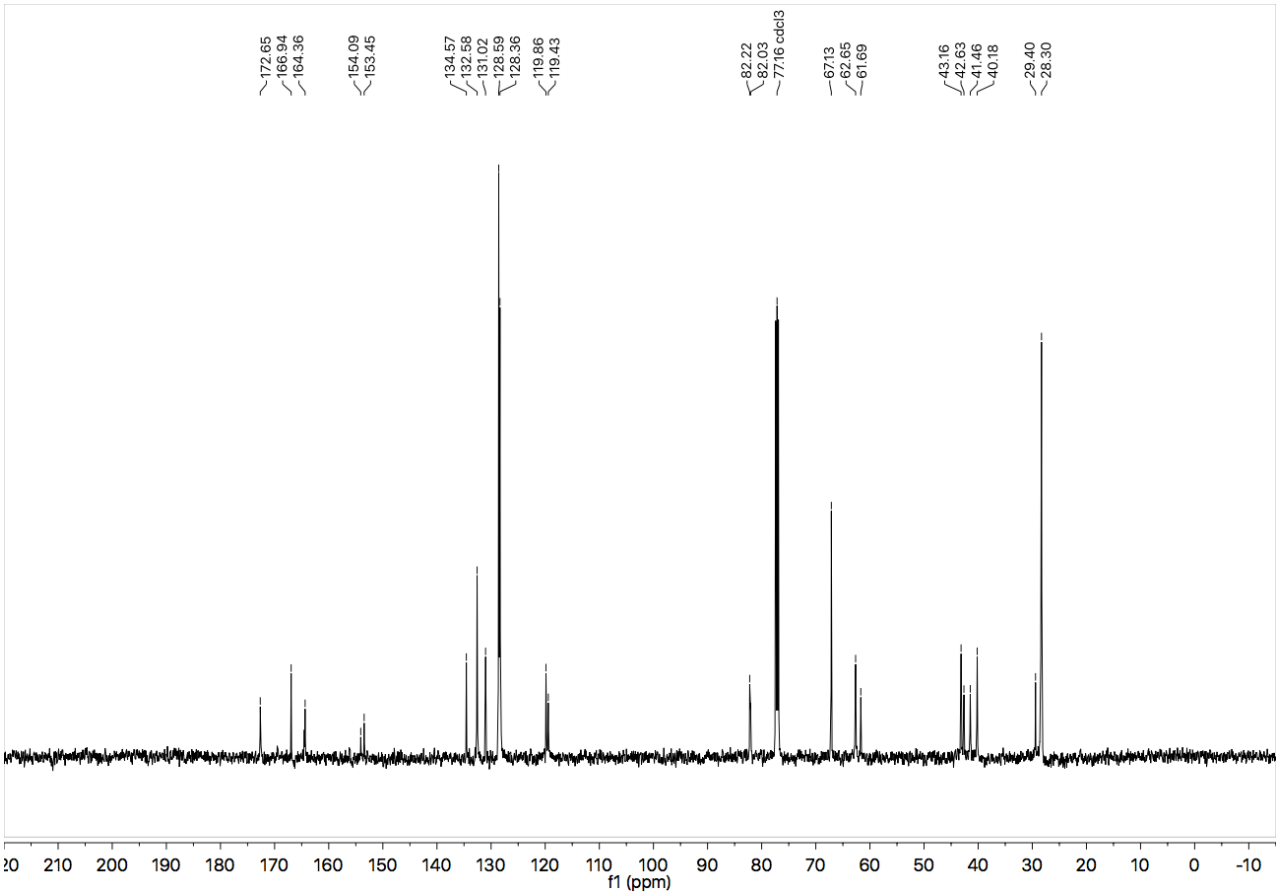
(11) A. Chollet, G. Mori, C. Menendez, F. Rodriguez, I. Fabing, M. R. Pasca, J. Madacki, J. Korduláková, P. Constant, A. Quémard, et al., *Eur. J. Med. Chem.* **2015**, *101*, 218–235.



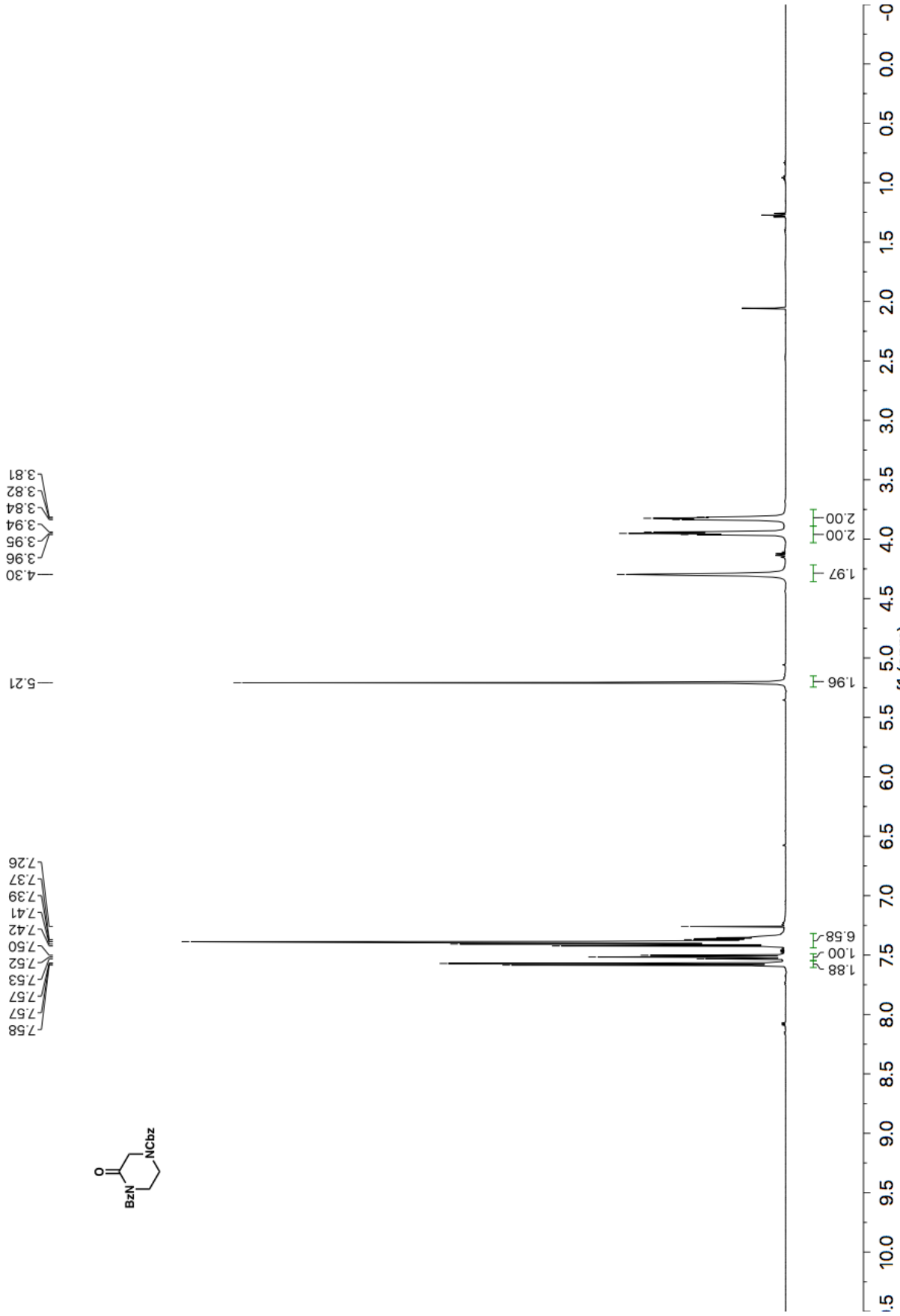
^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.**



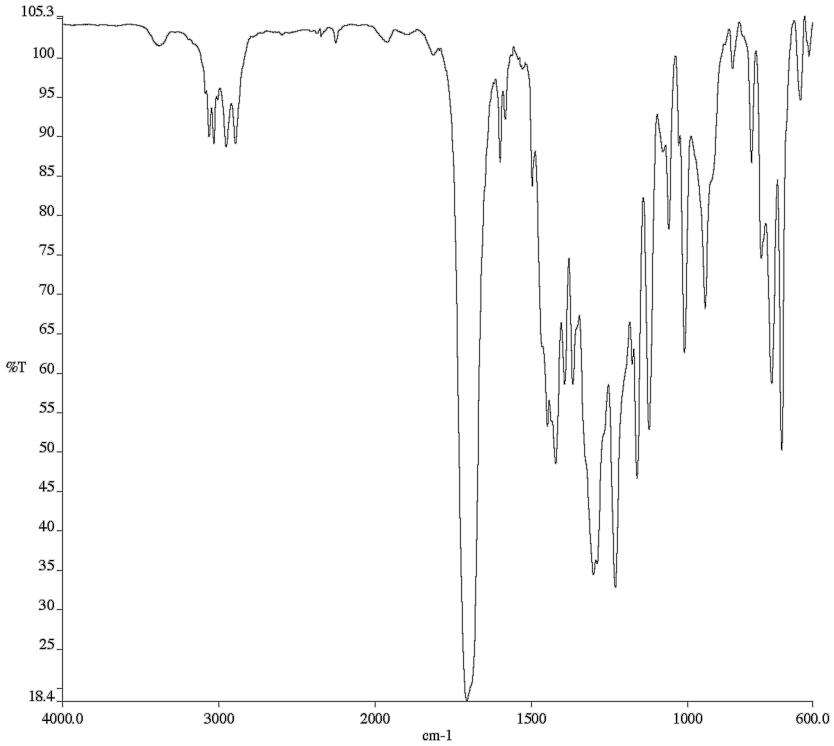
Infrared spectrum (Thin Film, NaCl) of compound **2**.



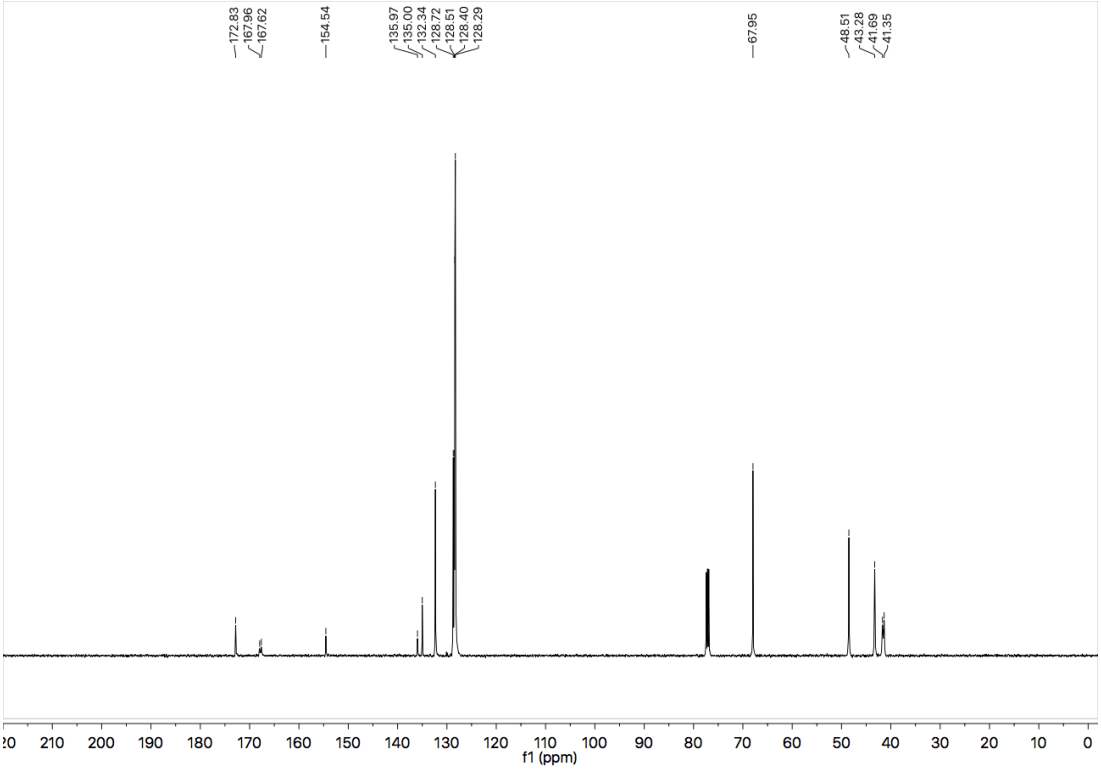
^{13}C NMR (126 MHz, $CDCl_3$) of compound **2**.



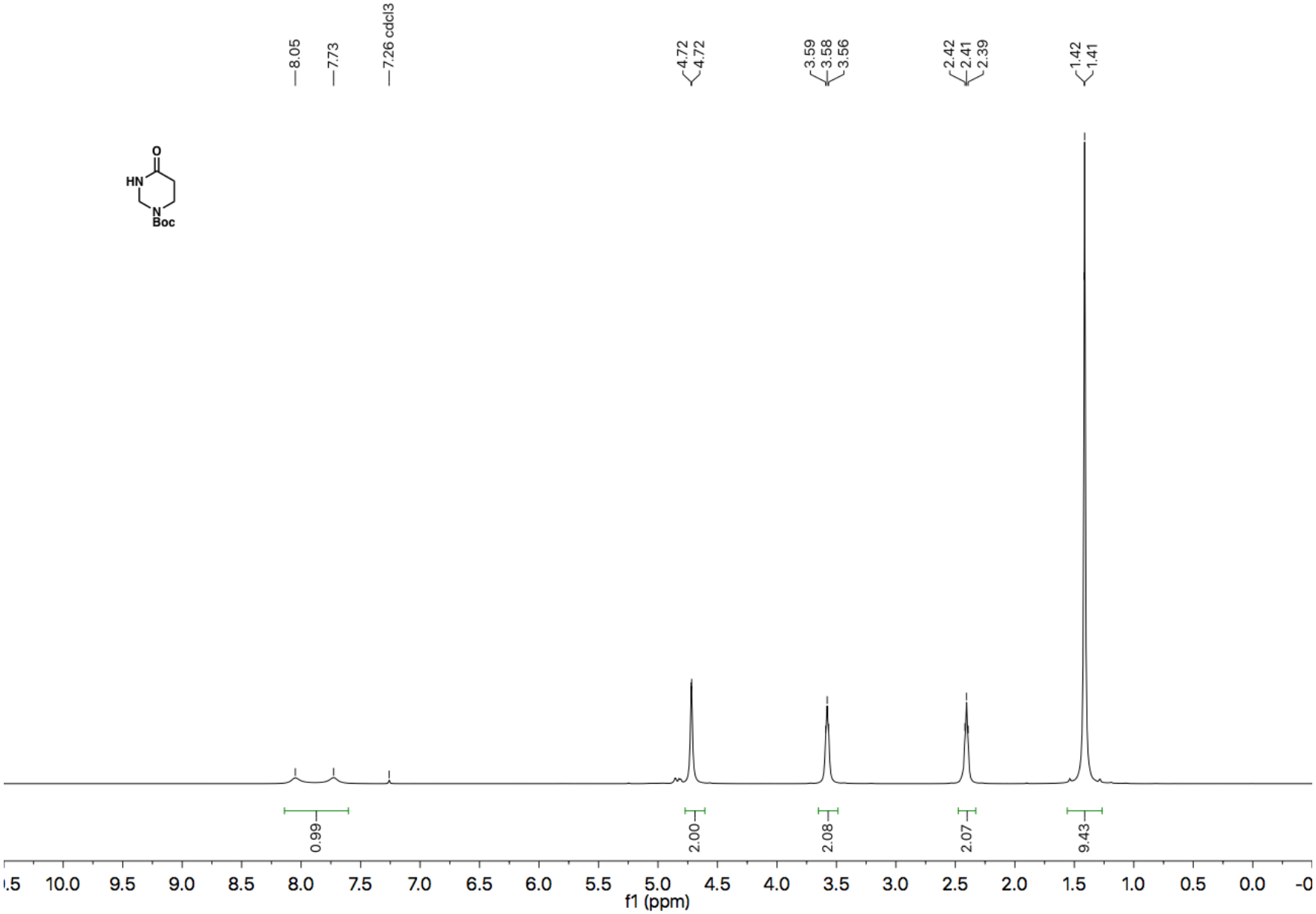
^{1}H NMR (500 MHz, $CDCl_3$) of compound **SI-3.**



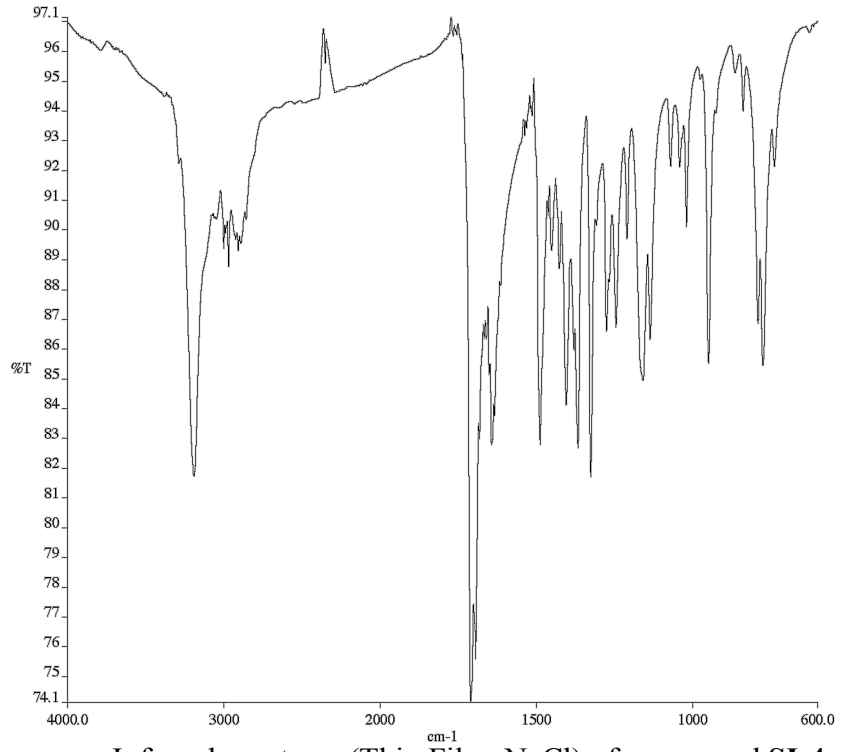
Infrared spectrum (Thin Film, NaCl) of compound **SI-3**.



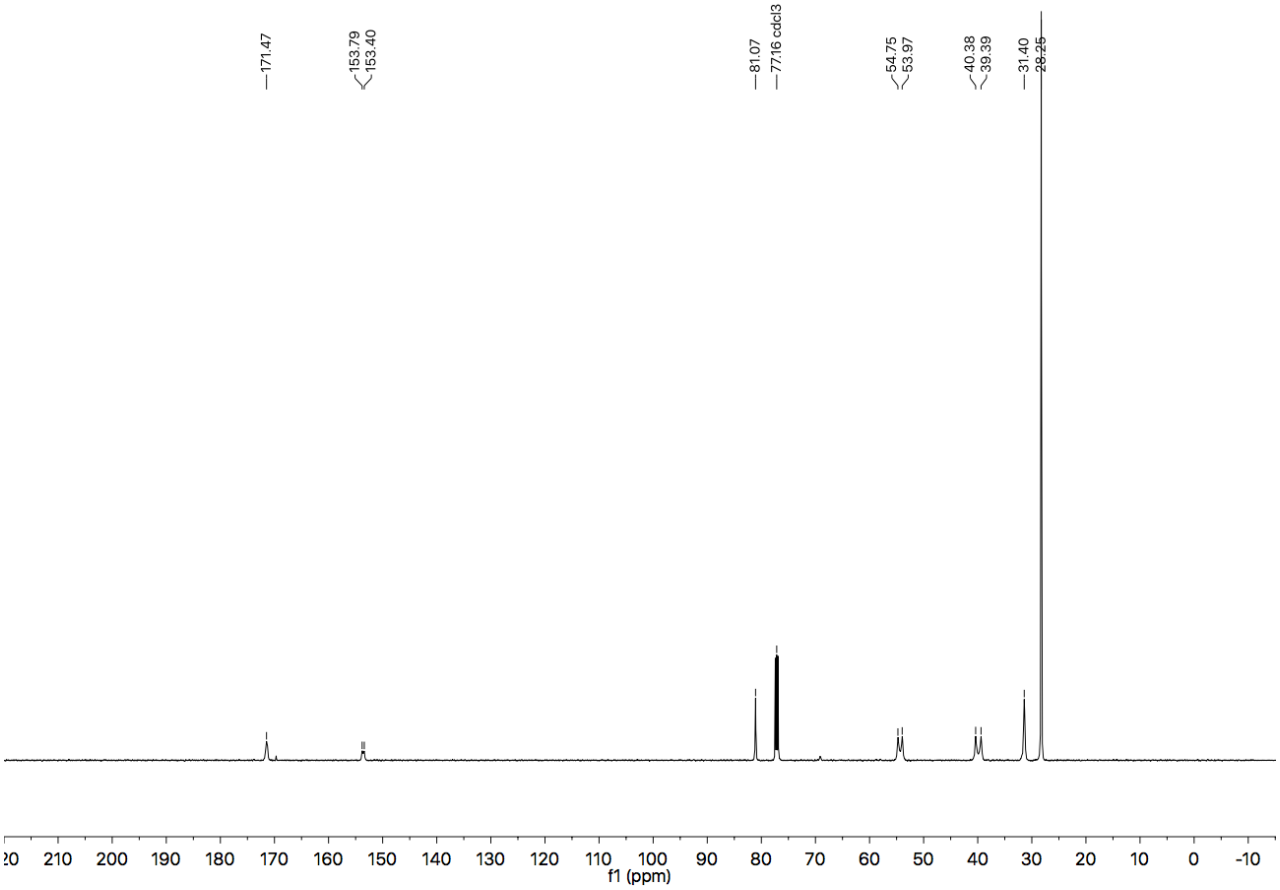
^{13}C NMR (126 MHz, $CDCl_3$) of compound **SI-3**.



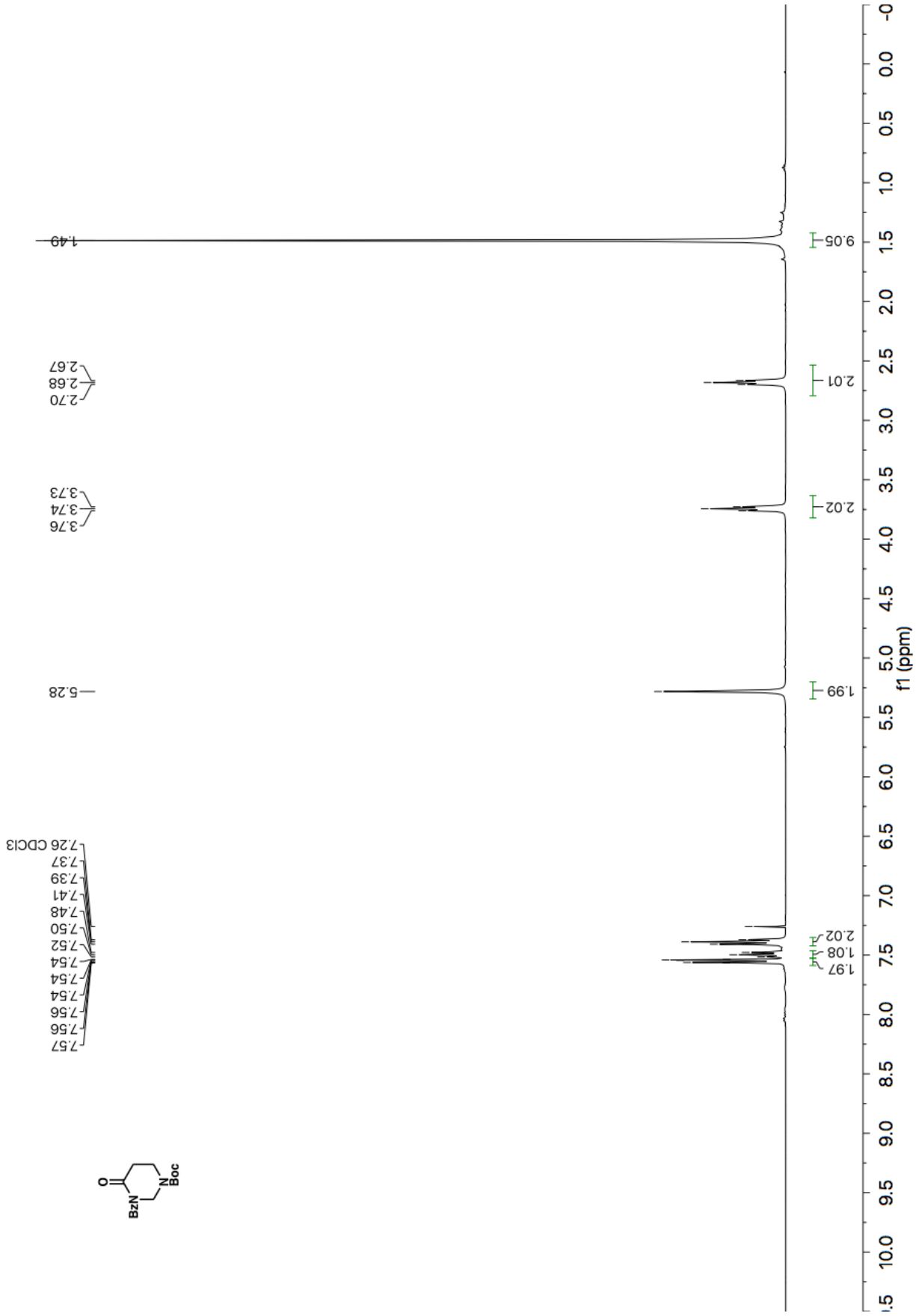
^{1}H NMR (500 MHz, $CDCl_3$) of compound **SI-4.**



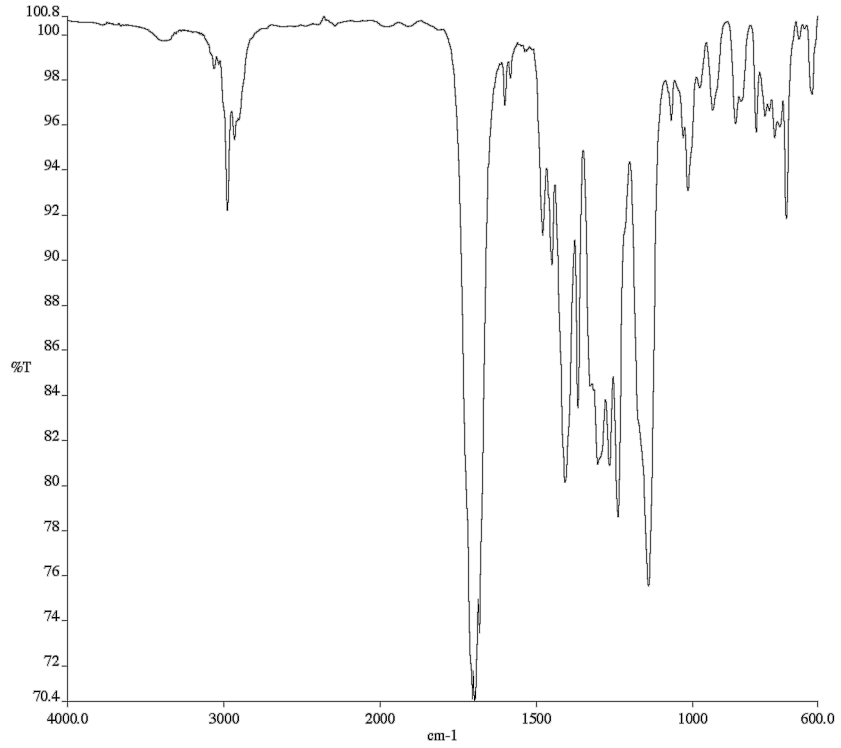
Infrared spectrum (Thin Film, NaCl) of compound **SI-4**.



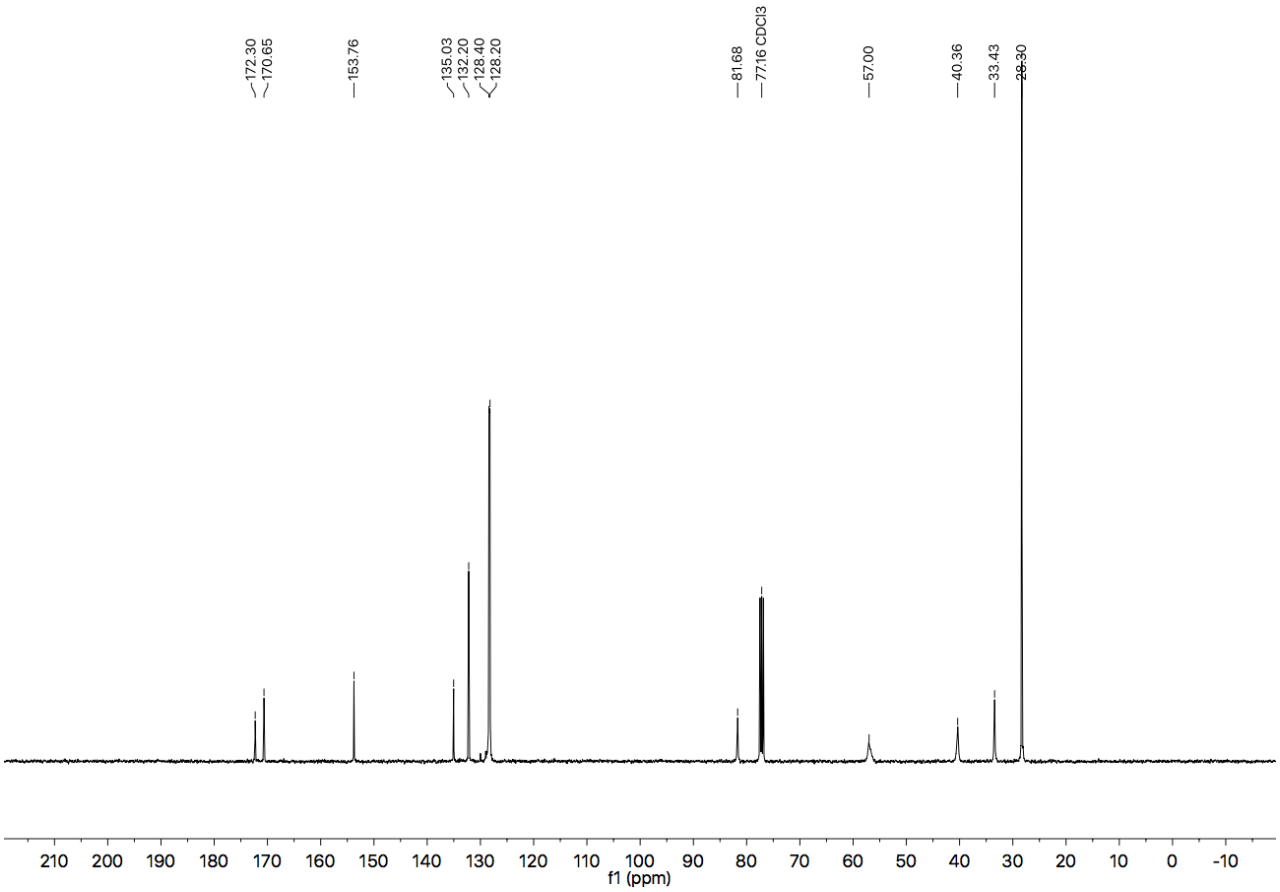
^{13}C NMR (126 MHz, $CDCl_3$) of compound **SI-4**.



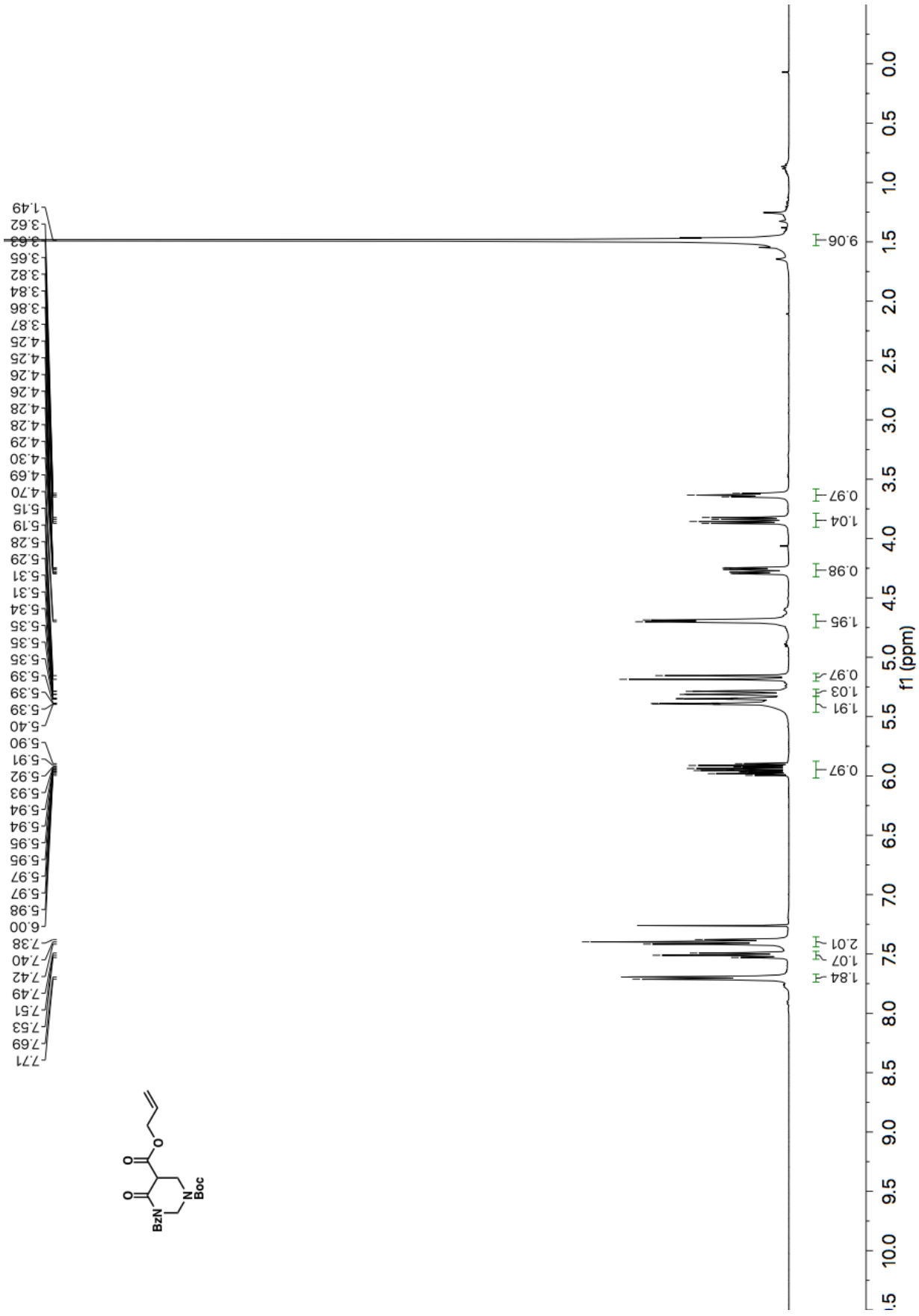
^{1}H NMR (400 MHz, $CDCl_3$) of compound **SI-5.**



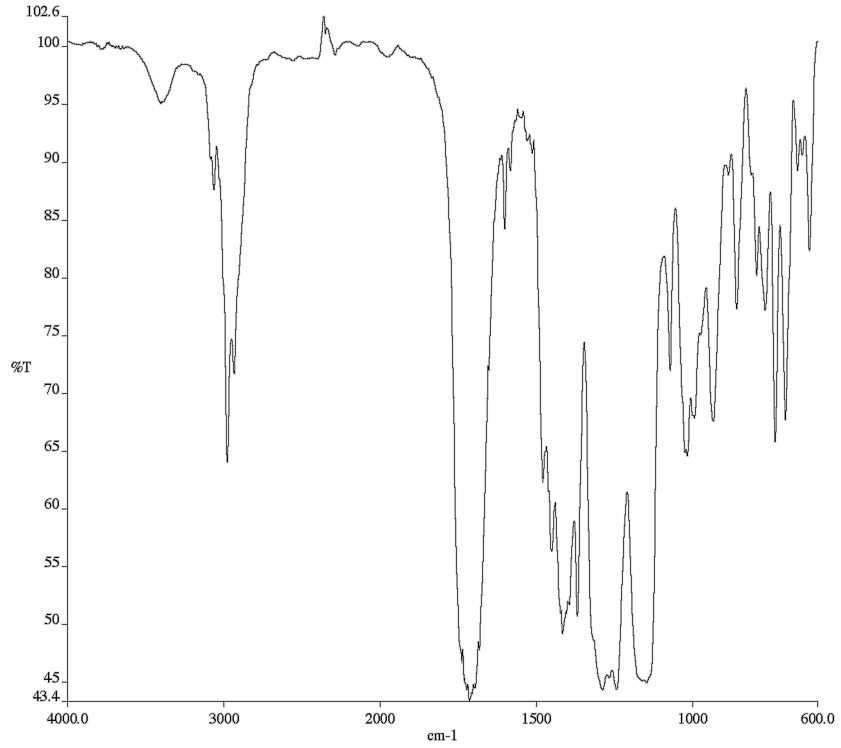
Infrared spectrum (Thin Film, NaCl) of compound **SI-5**.



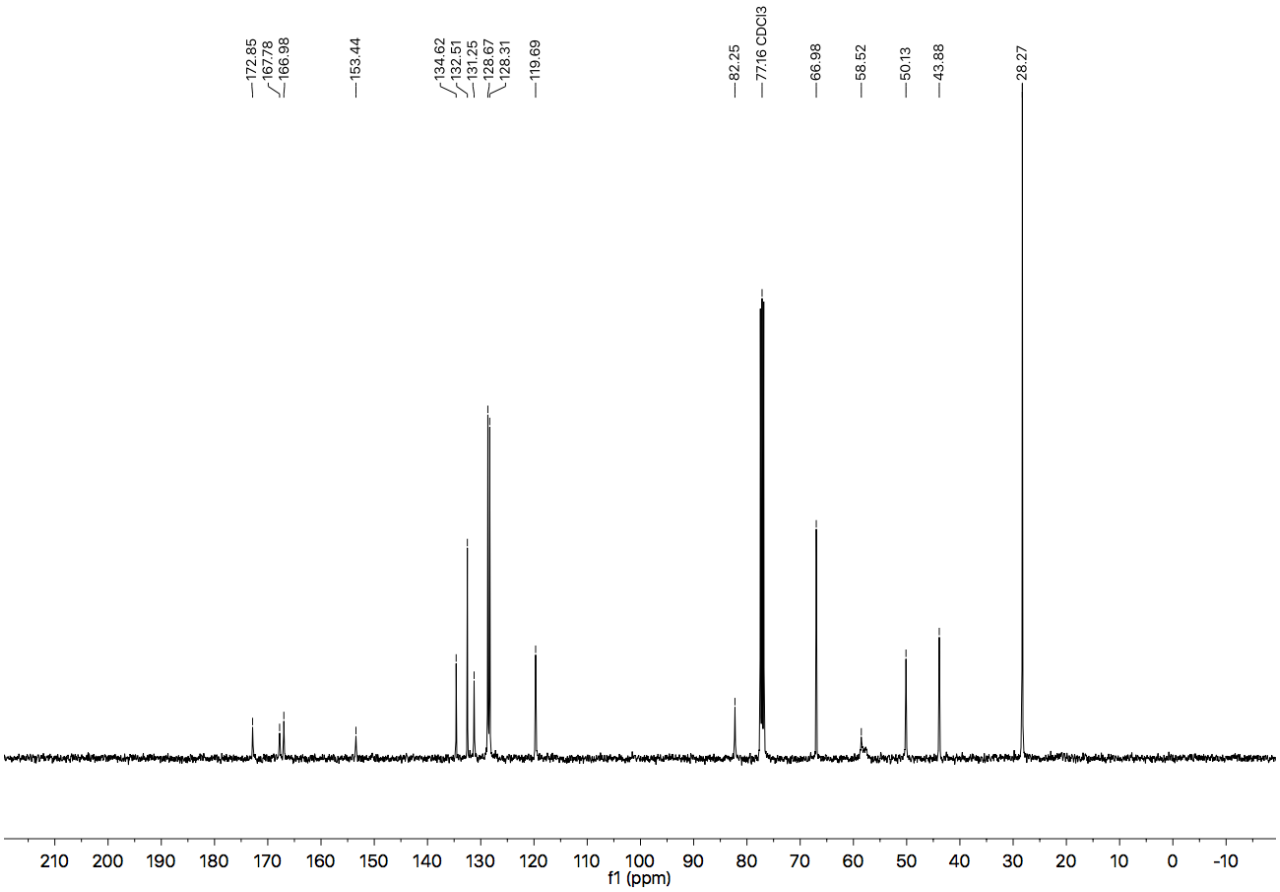
^{13}C NMR (101 MHz, $CDCl_3$) of compound **SI-5**.



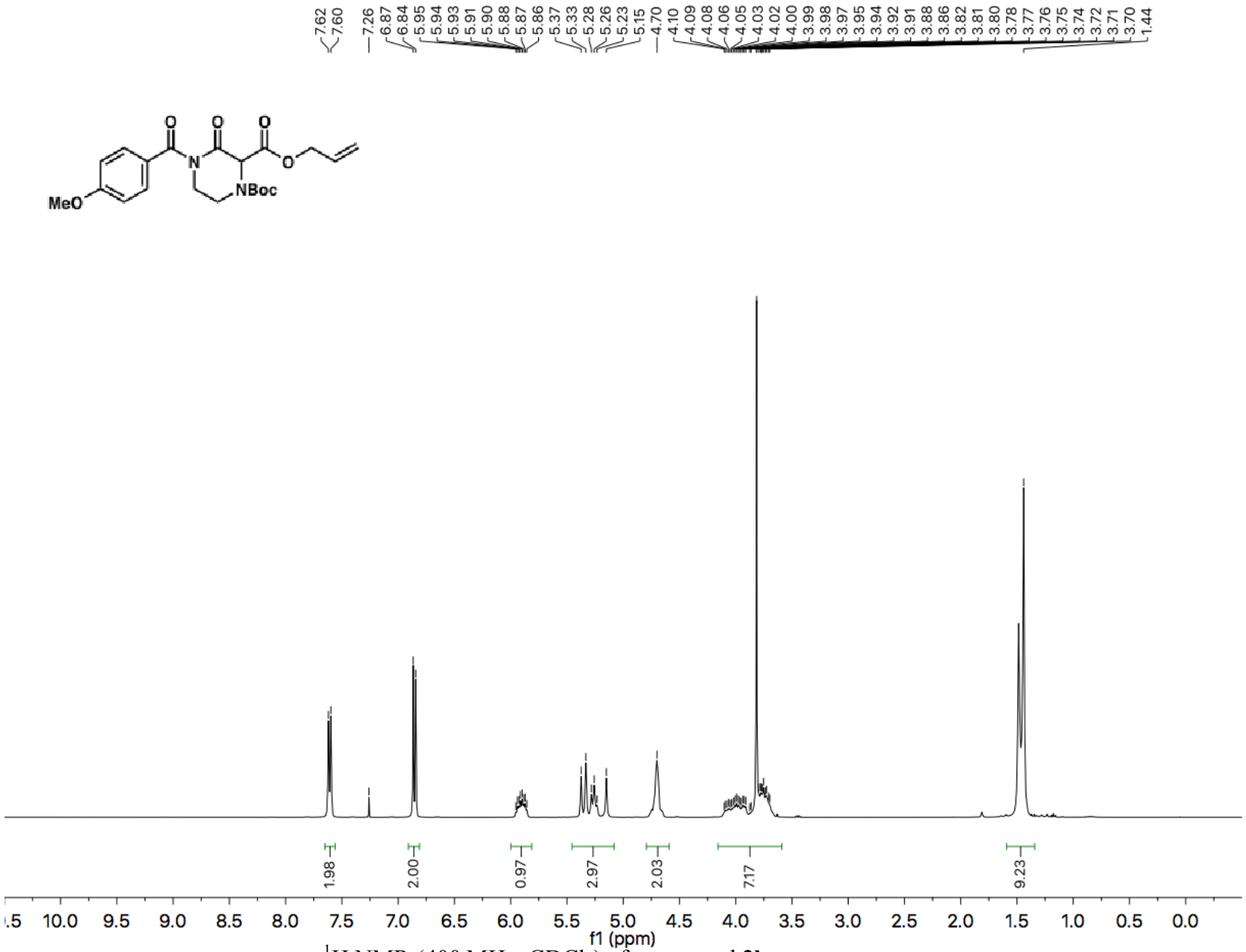
^{1}H NMR (400 MHz, $CDCl_3$) of compound **SI-6.**



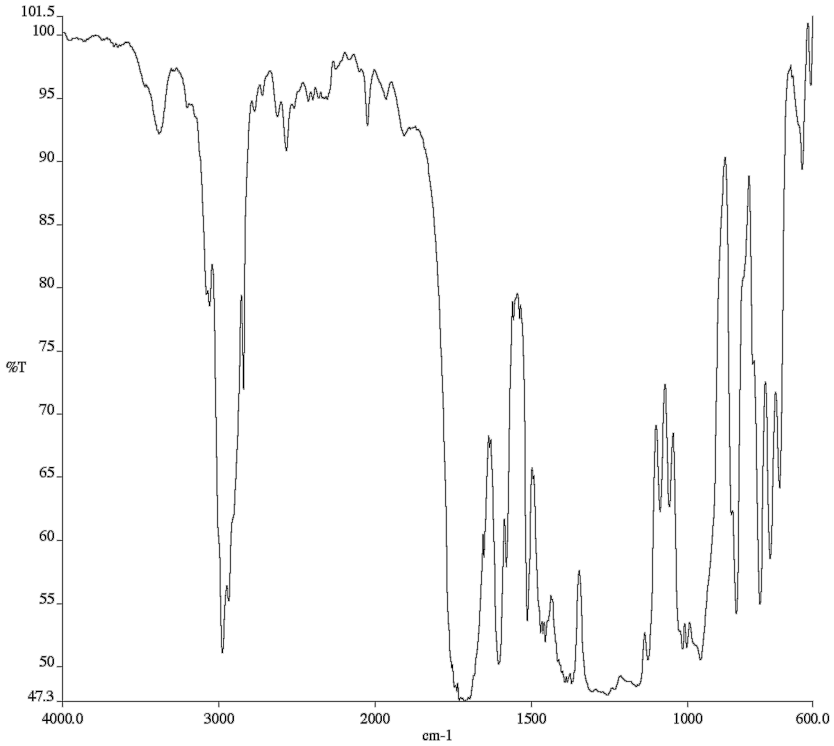
Infrared spectrum (Thin Film, NaCl) of compound **SI-6**.



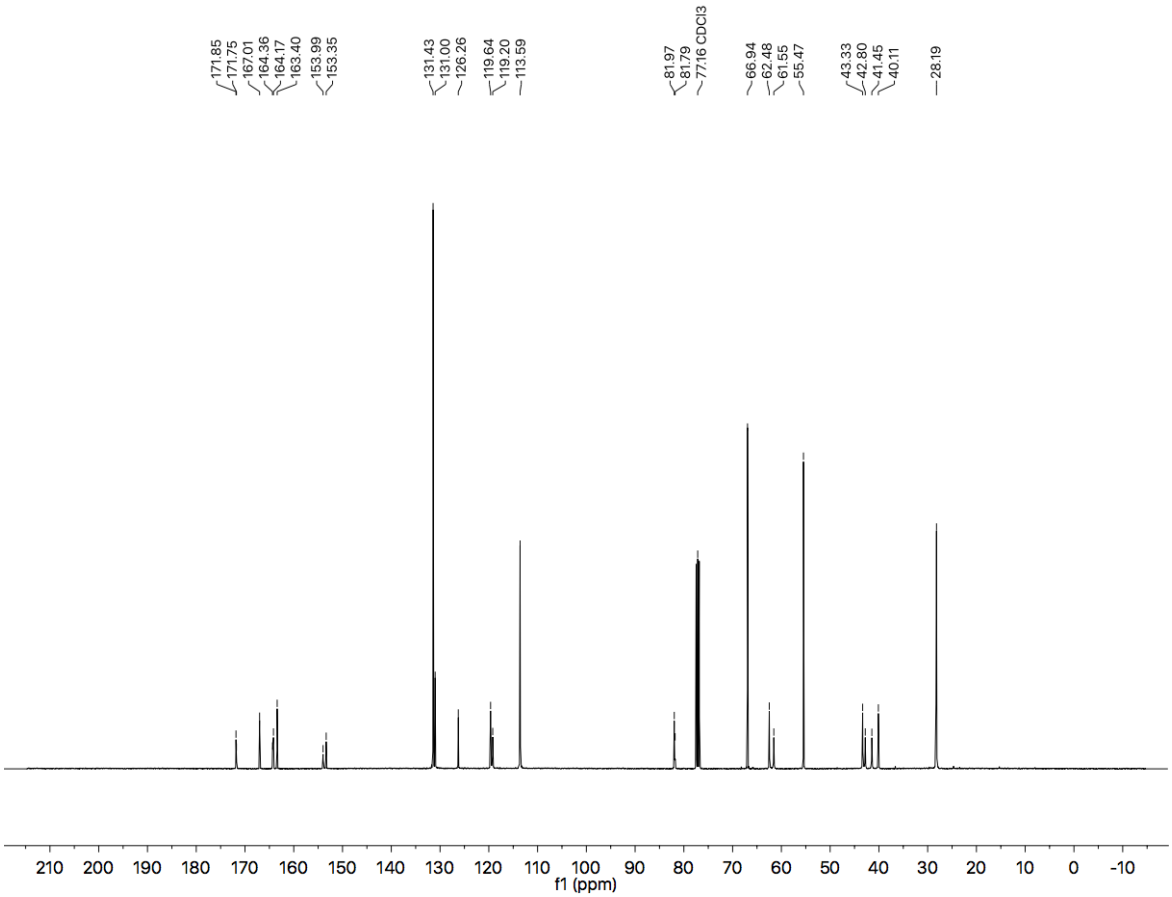
^{13}C NMR (101 MHz, $CDCl_3$) of compound **SI-6**.



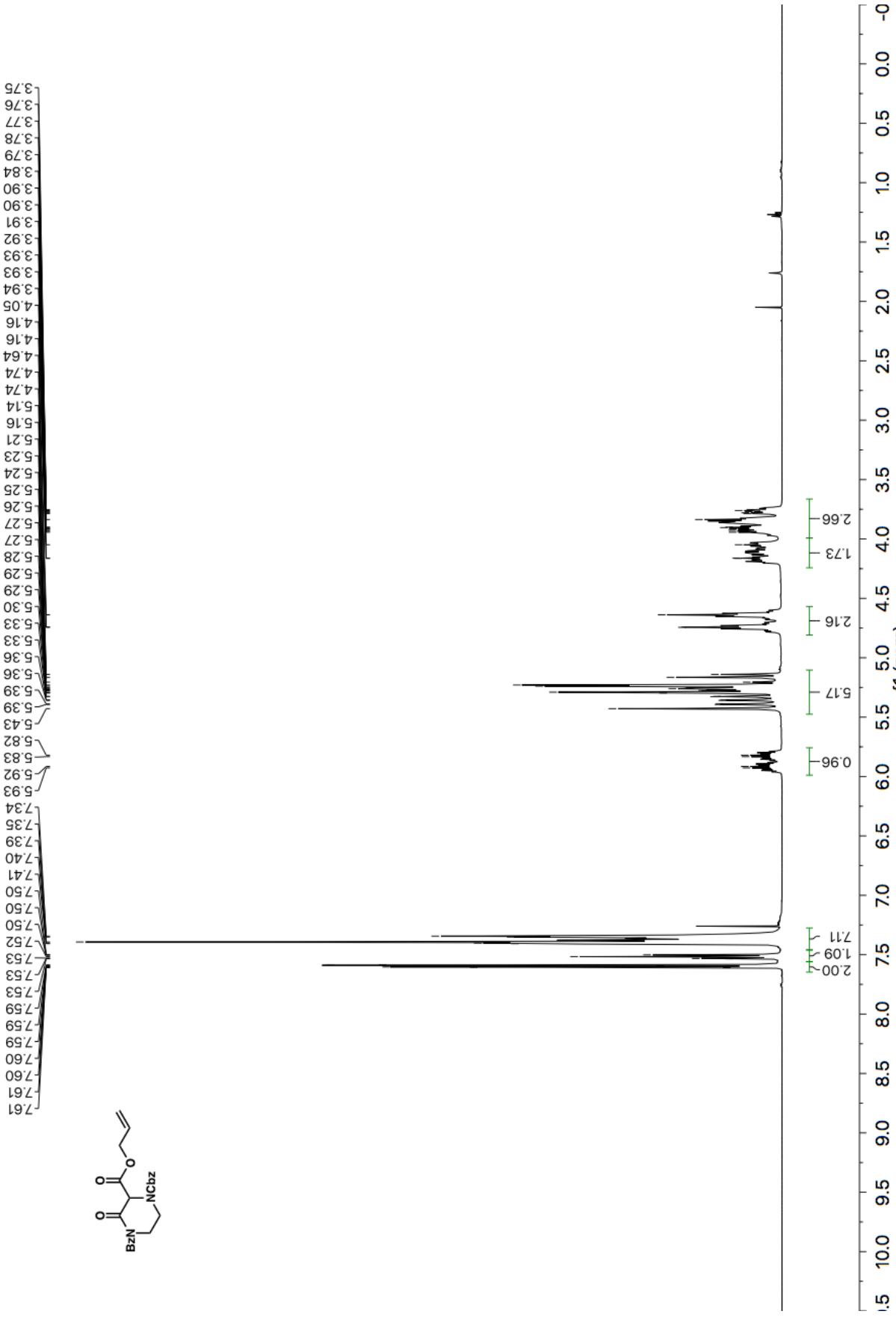
^{1}H NMR (400 MHz, $CDCl_3$) of compound **3b.**



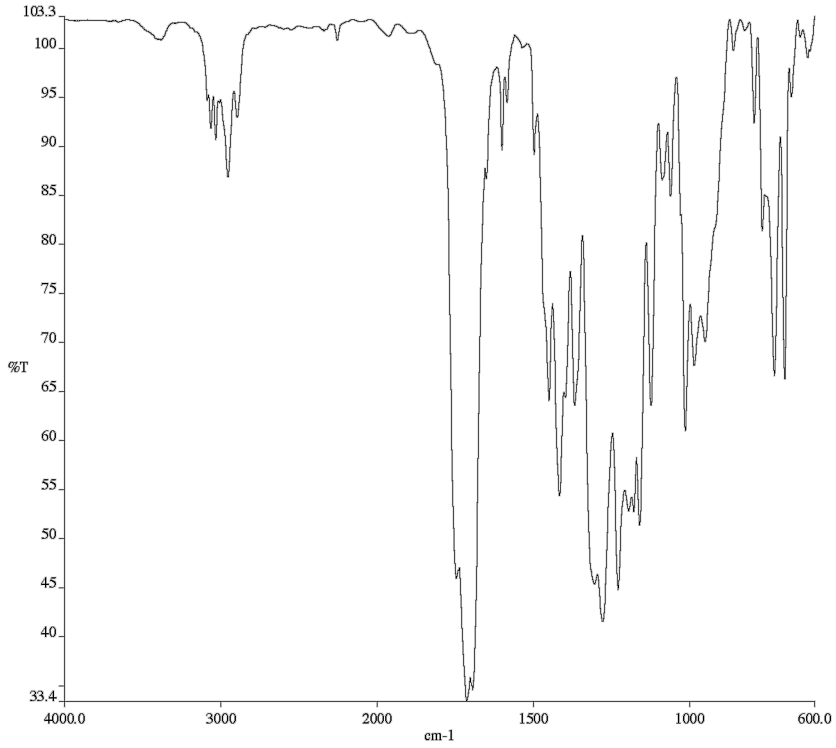
Infrared spectrum (Thin Film, NaCl) of compound **3b**.



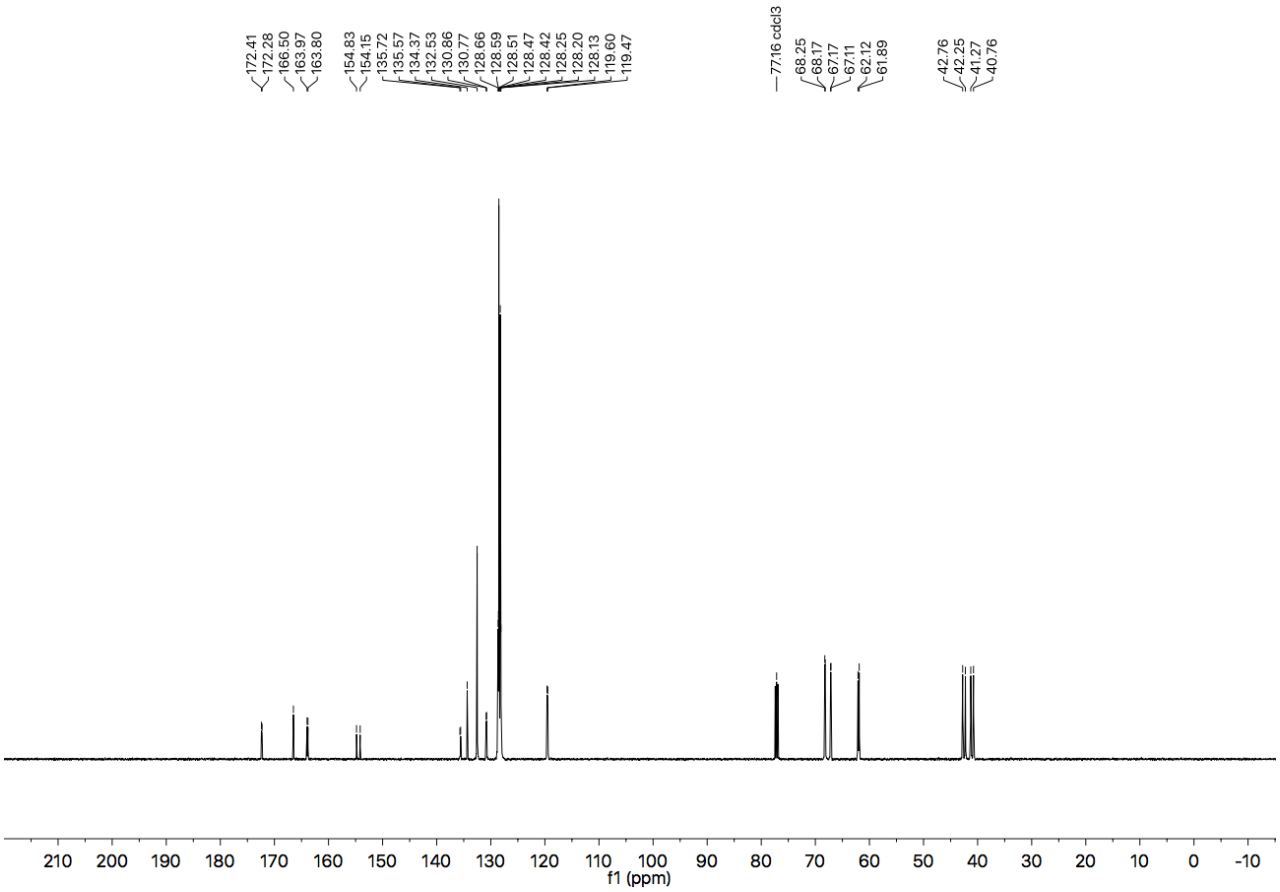
^{13}C NMR (101 MHz, $CDCl_3$) of compound **3b**.



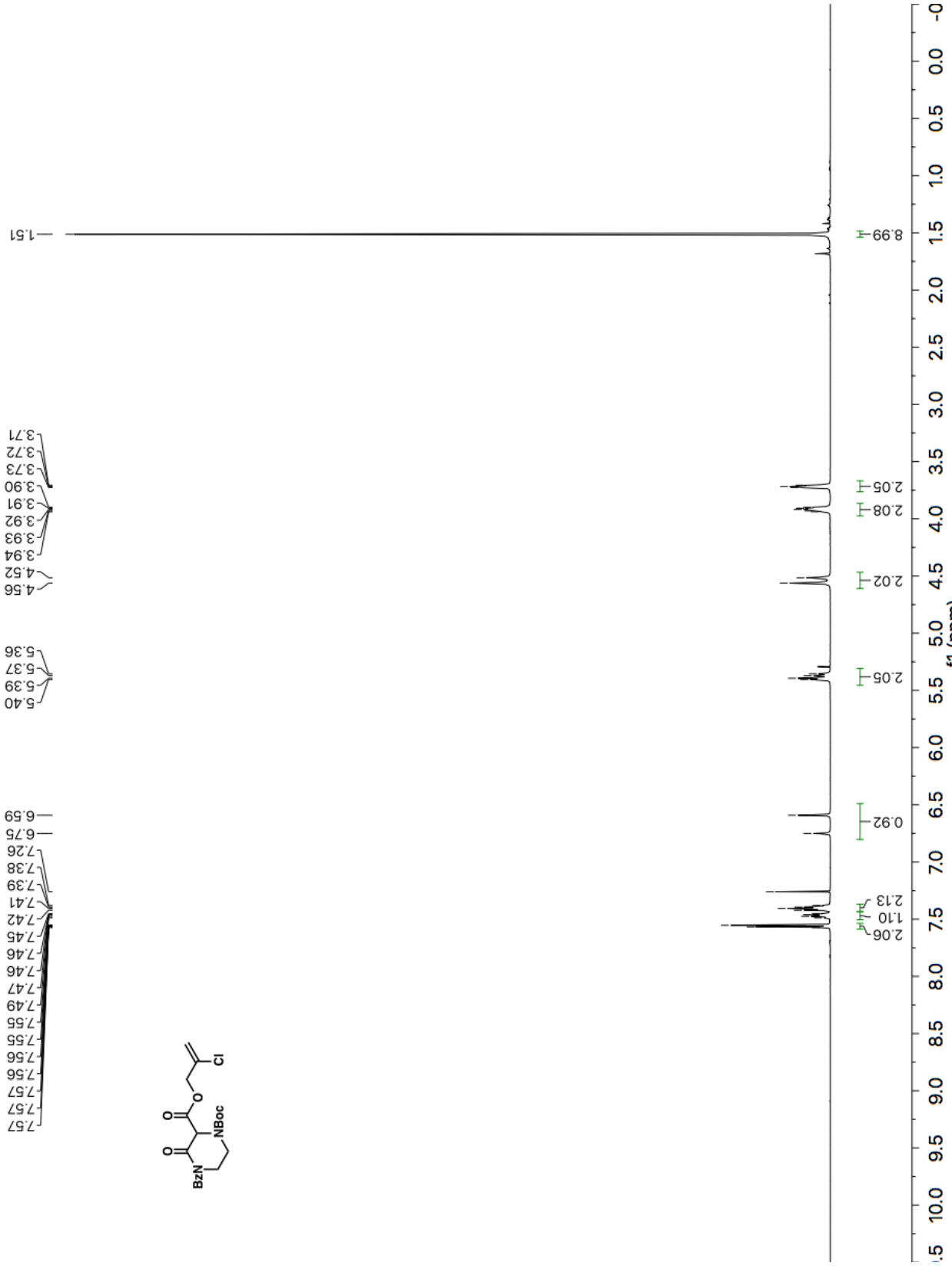
^{1}H NMR (500 MHz, $CDCl_3$) of compound **3c.**



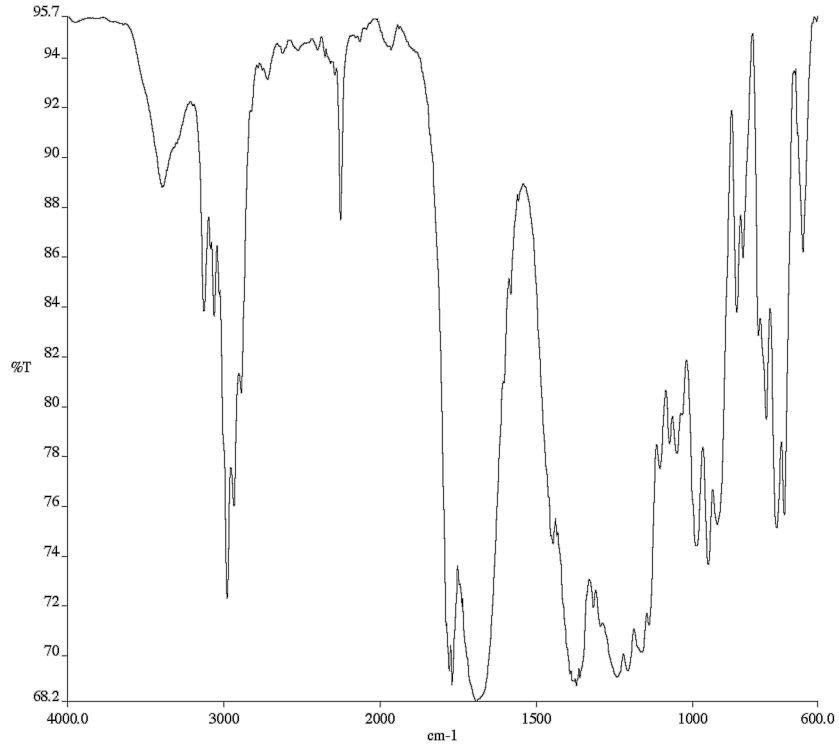
Infrared spectrum (Thin Film, NaCl) of compound **3c**.



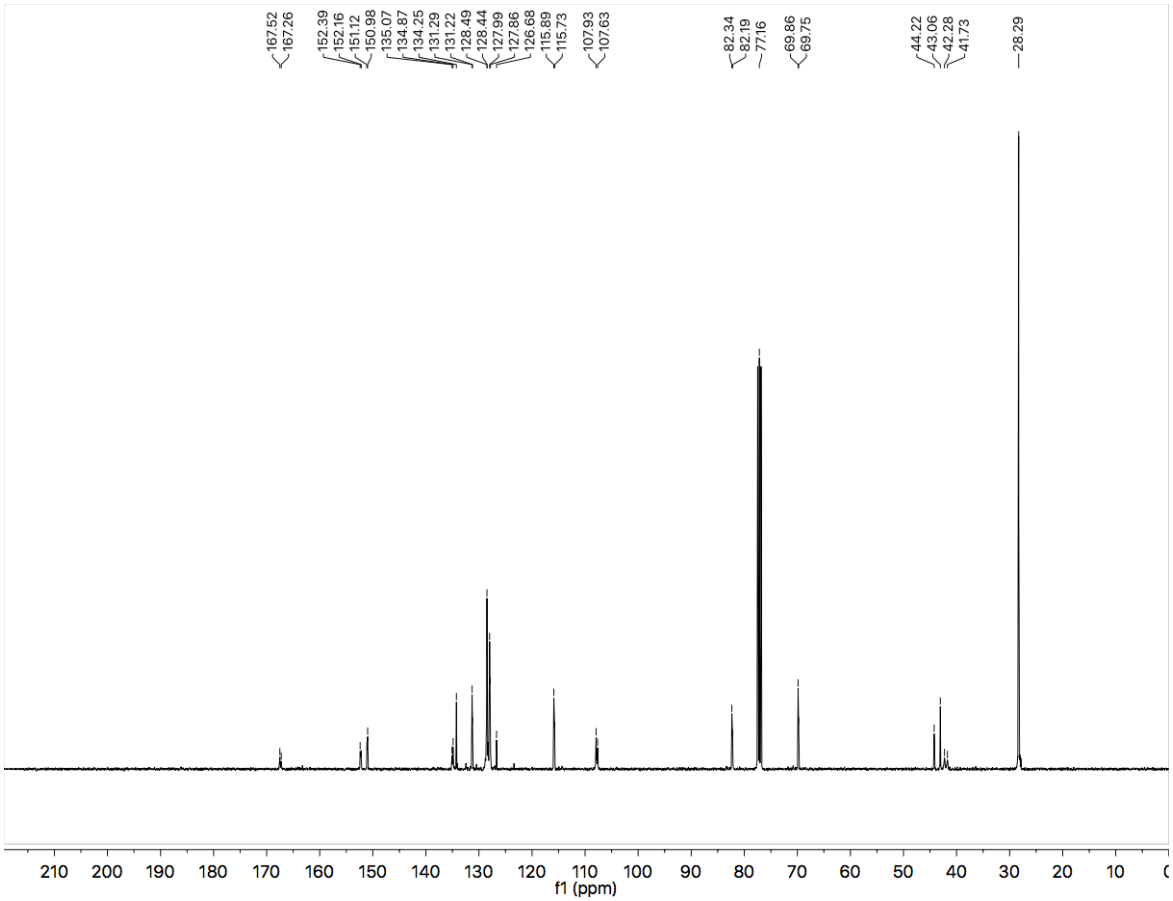
^{13}C NMR (126 MHz, $CDCl_3$) of compound **3c**.



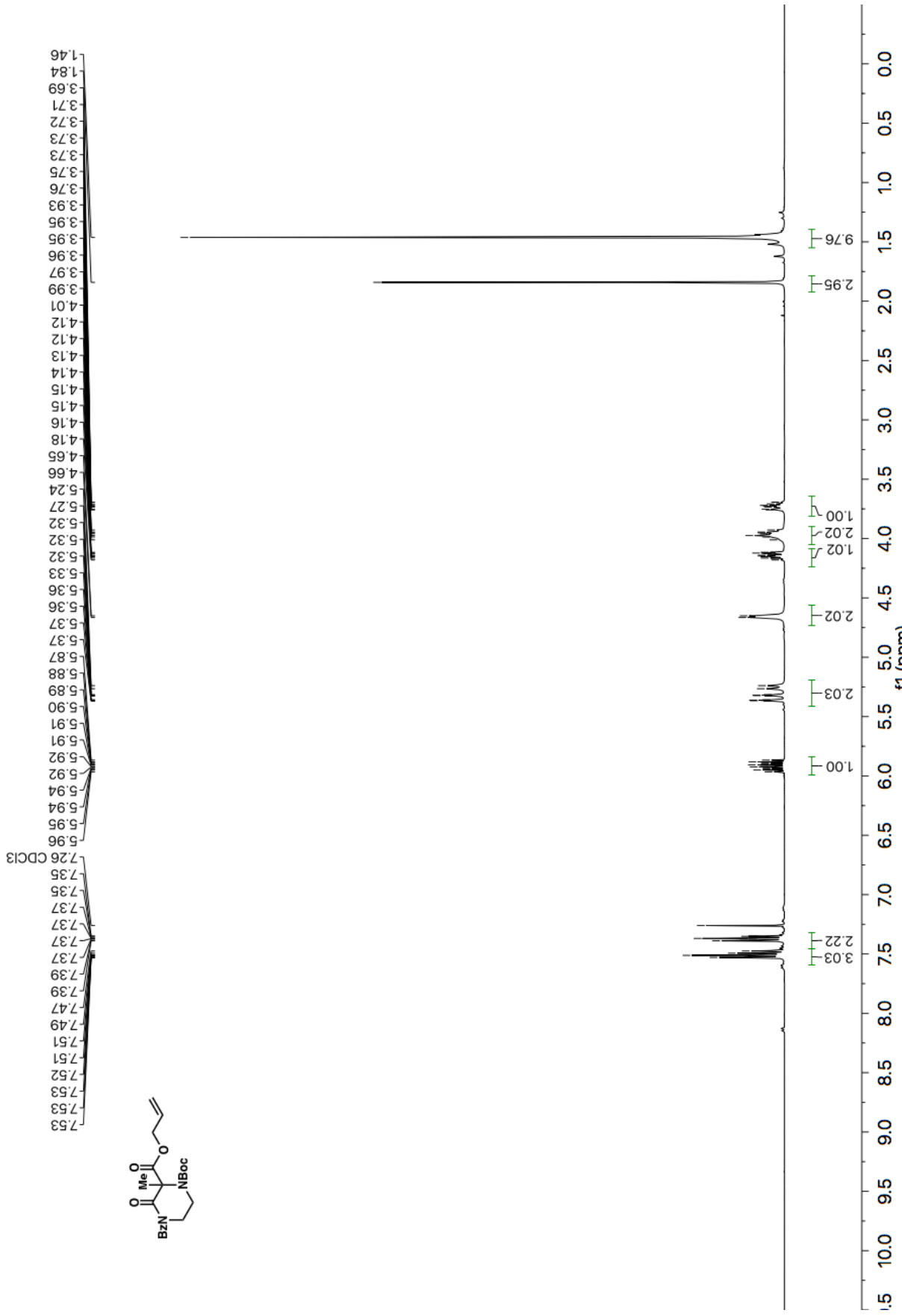
^{1}H NMR (400 MHz, $CDCl_3$) of compound **3d.**



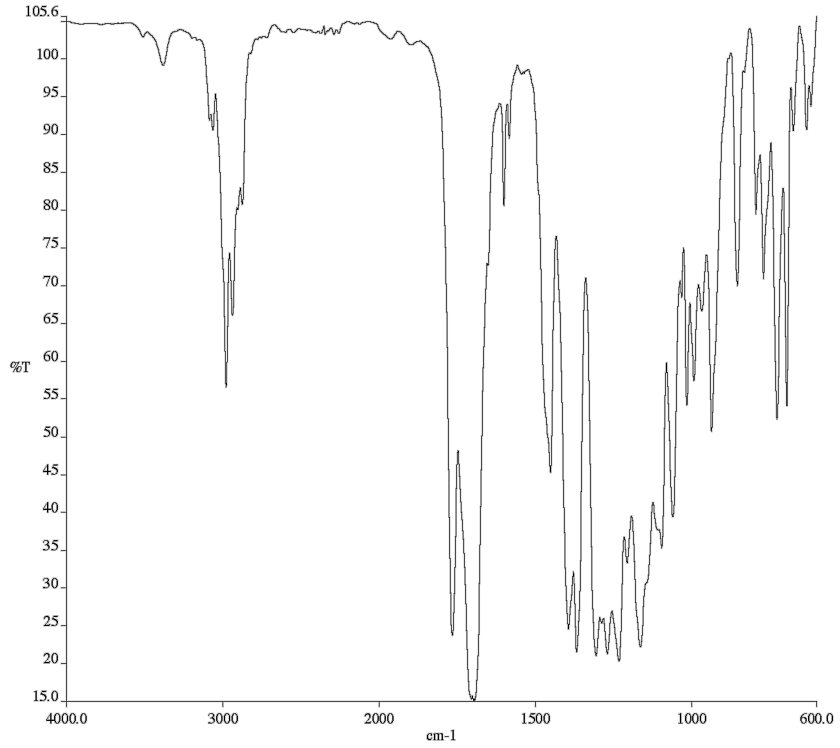
Infrared spectrum (Thin Film, NaCl) of compound **3d**.



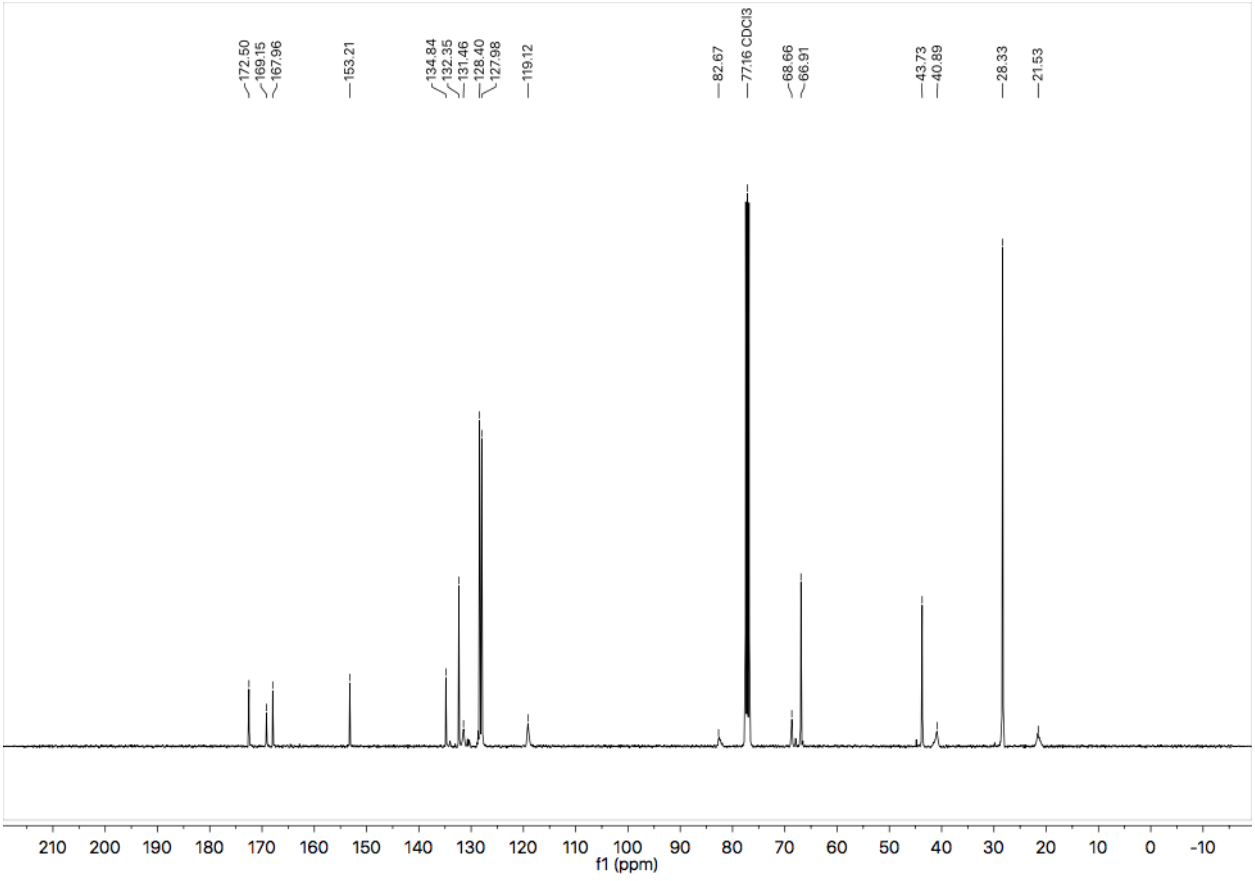
^{13}C NMR (101 MHz, $CDCl_3$) of compound **3d**.



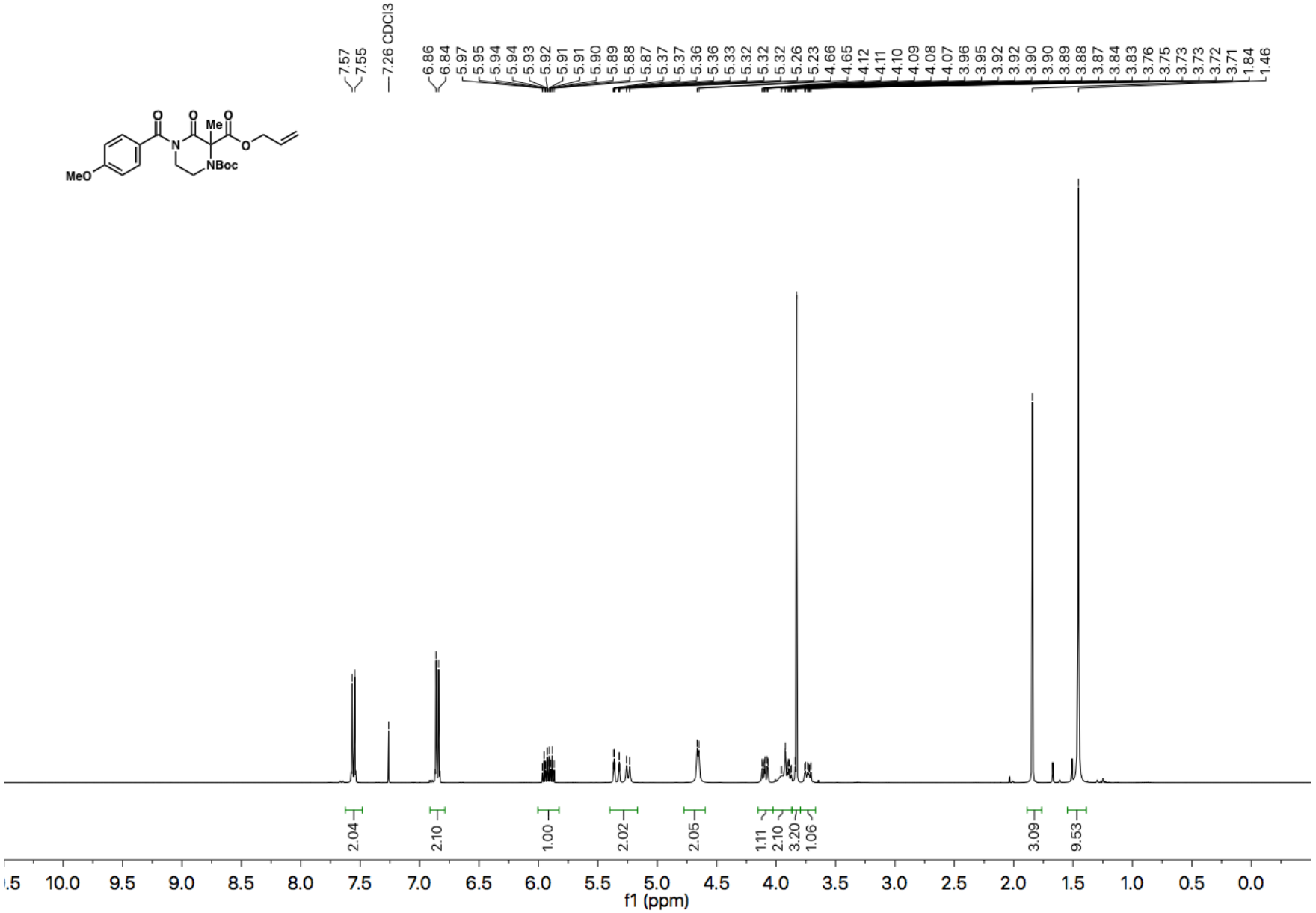
^{1}H NMR (400 MHz, $CDCl_3$) of compound **3e.**



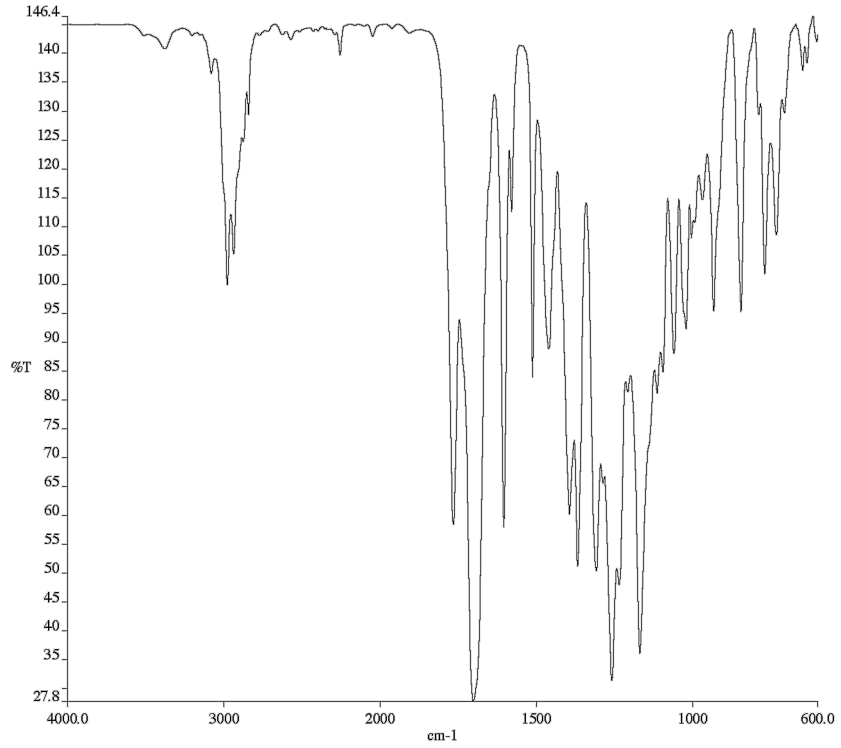
Infrared spectrum (Thin Film, NaCl) of compound **3e**.



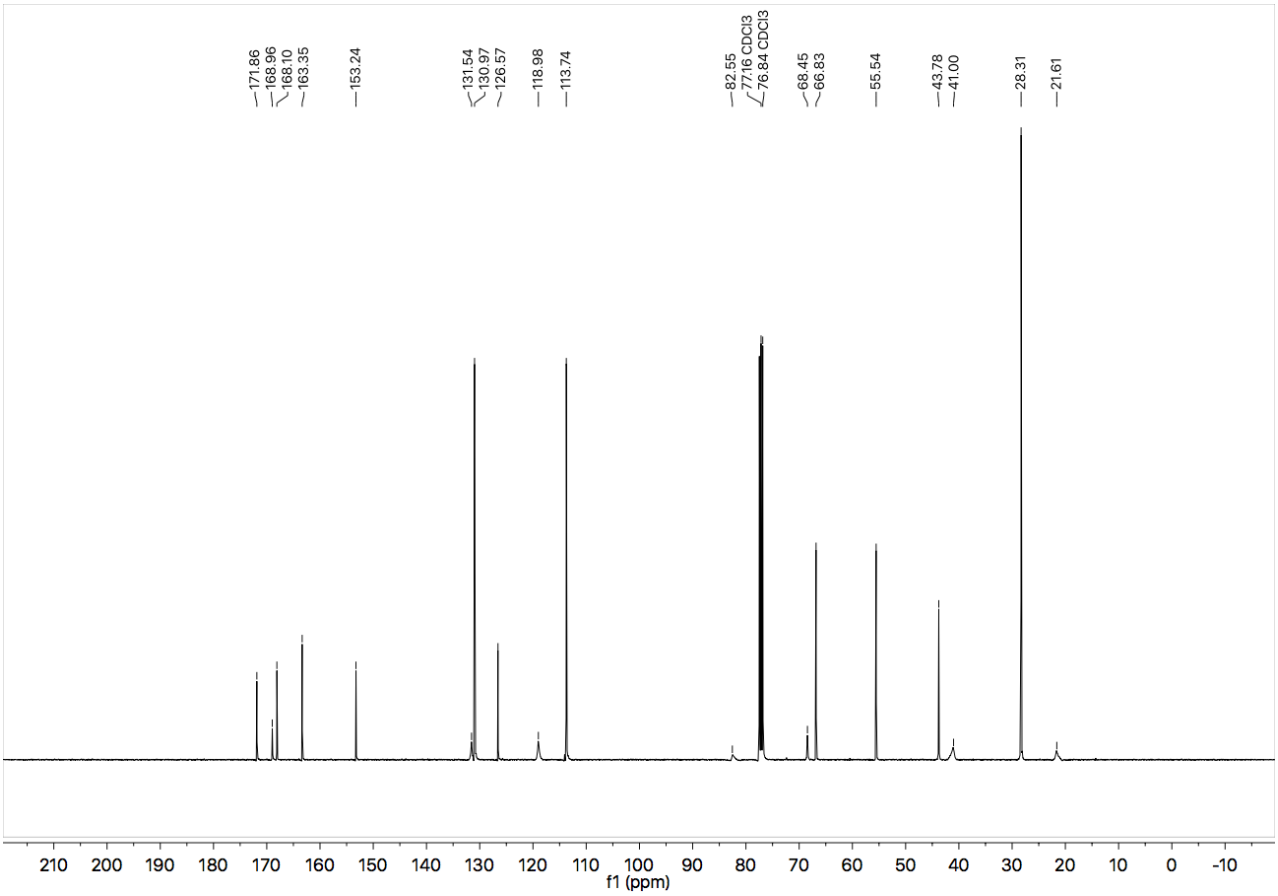
^{13}C NMR (101 MHz, $CDCl_3$) of compound **3e**.



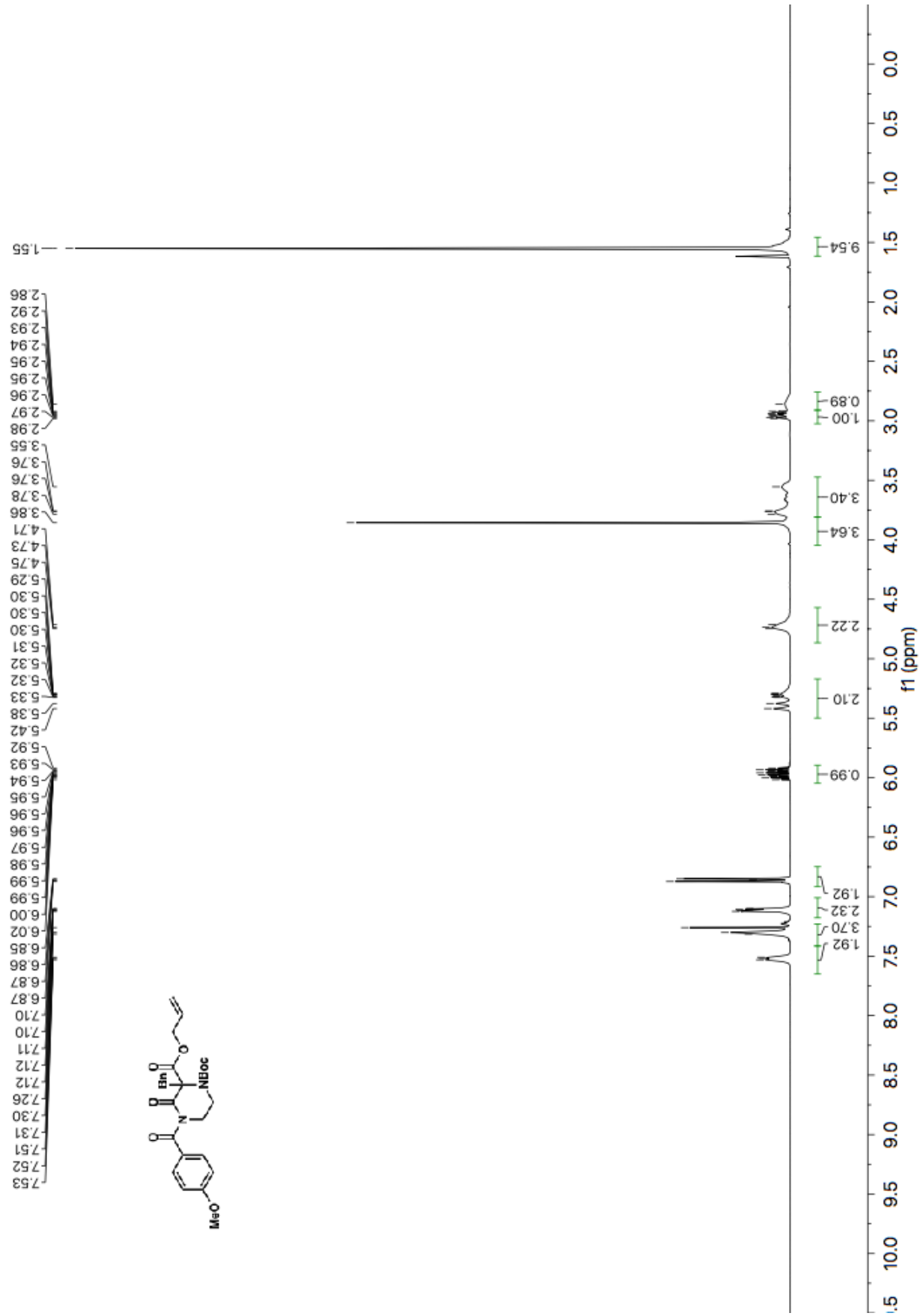
^{1}H NMR (400 MHz, $CDCl_3$) of compound **3f.**



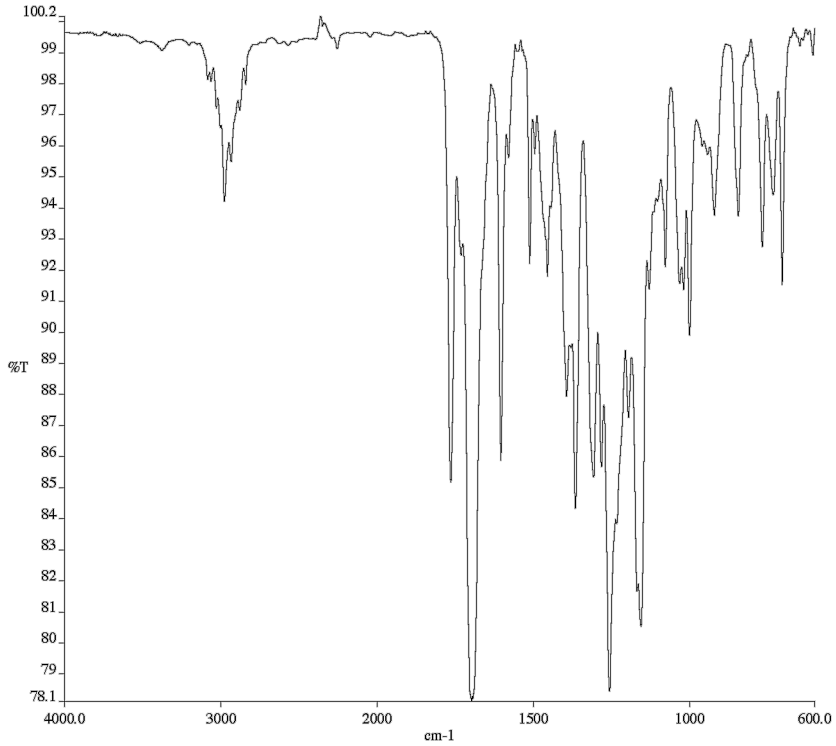
Infrared spectrum (Thin Film, NaCl) of compound **3f**.



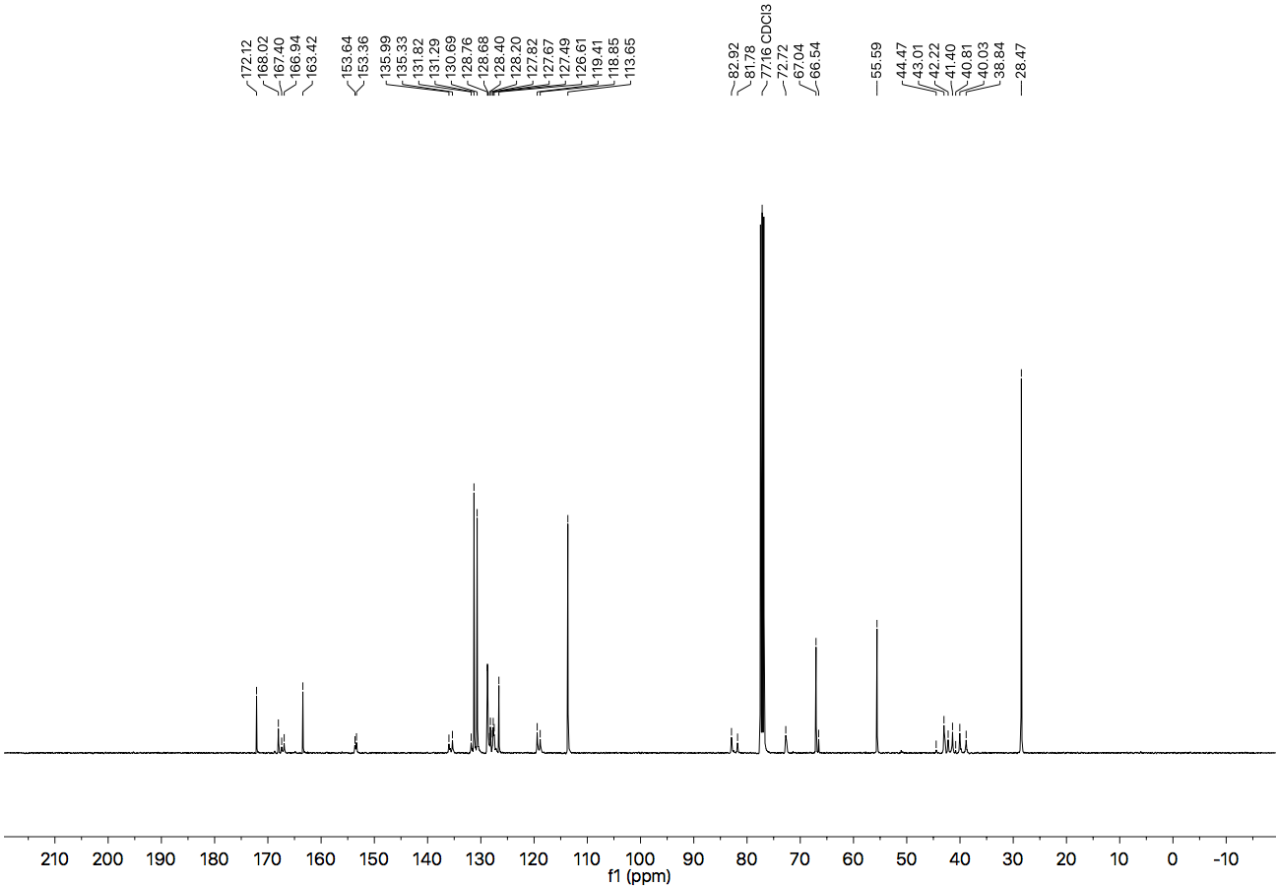
^{13}C NMR (101 MHz, $CDCl_3$) of compound **3f**.



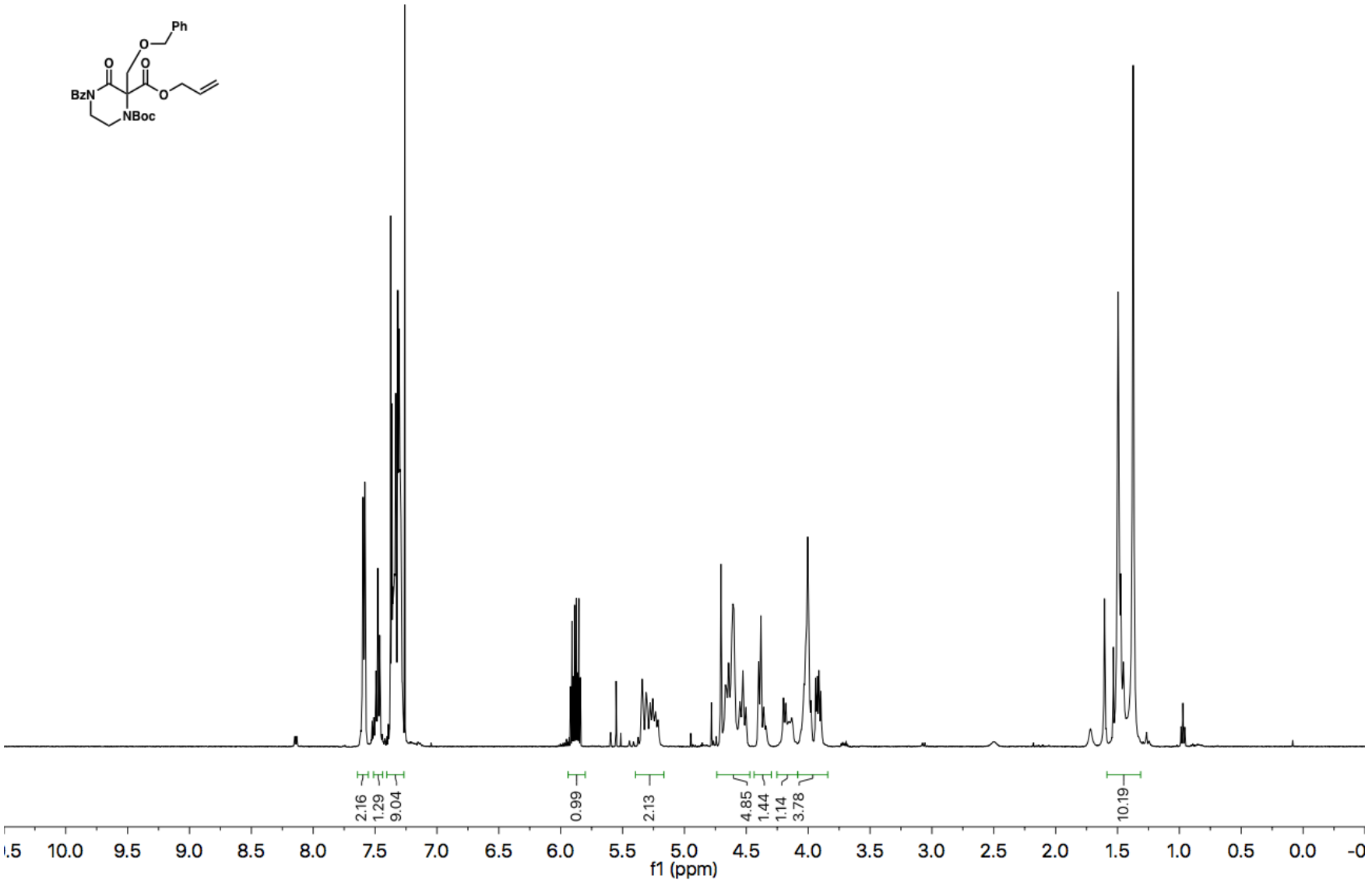
^{1}H NMR (400 MHz, $CDCl_3$) of compound **3h.**



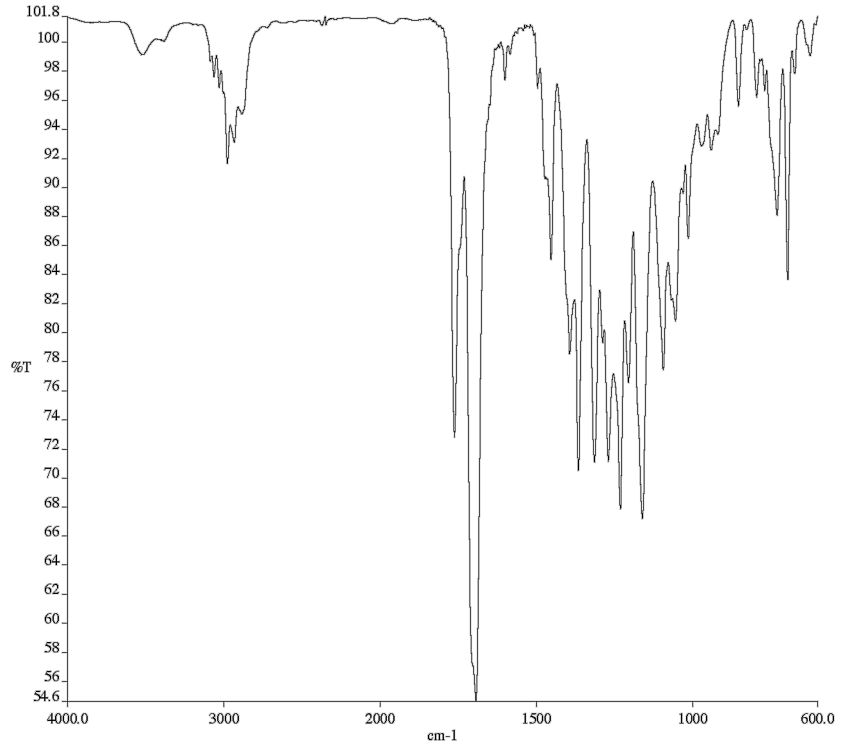
Infrared spectrum (Thin Film, NaCl) of compound **3h**.



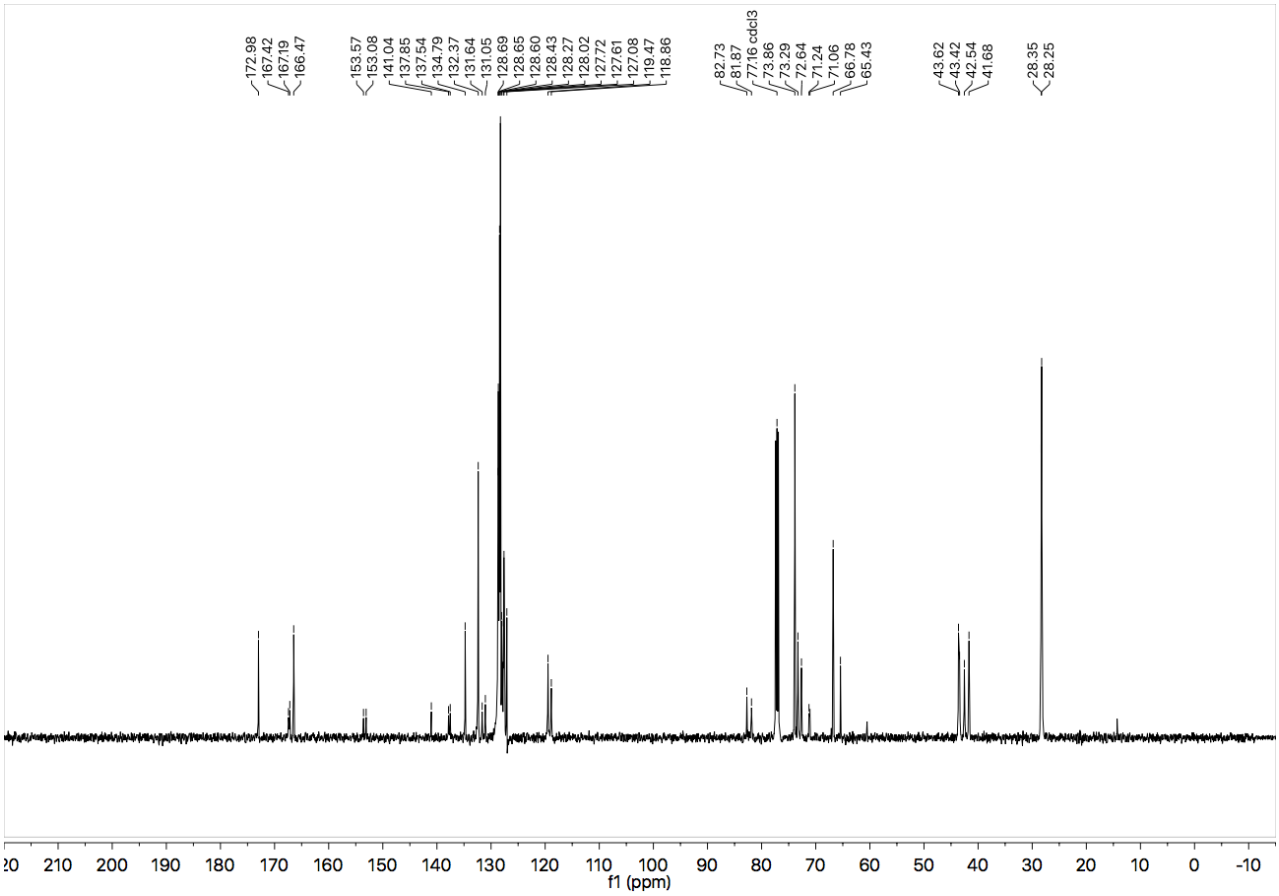
^{13}C NMR (101 MHz, $CDCl_3$) of compound **3h**.



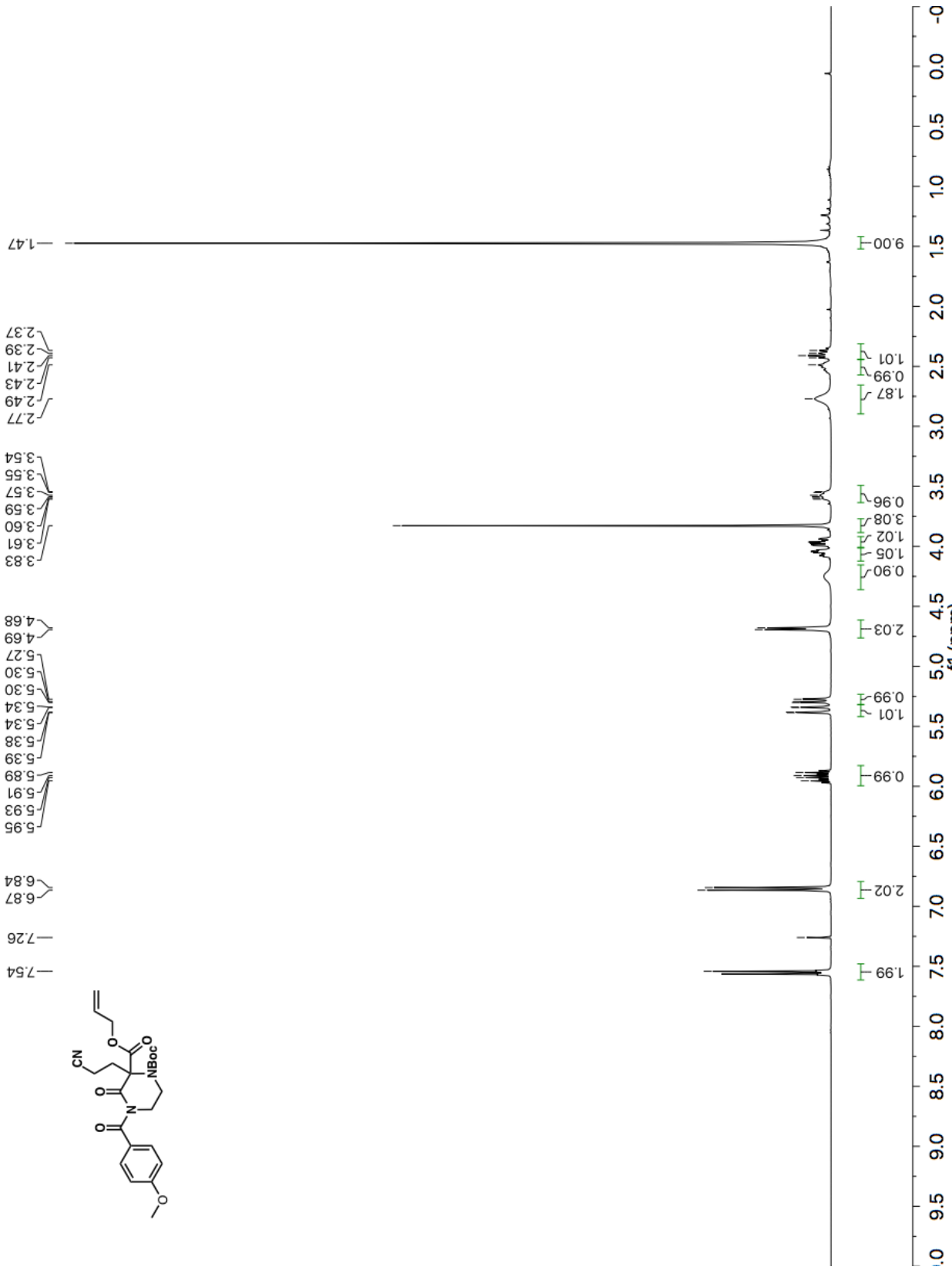
^{1}H NMR (500 MHz, $CDCl_3$) of compound **3i.**



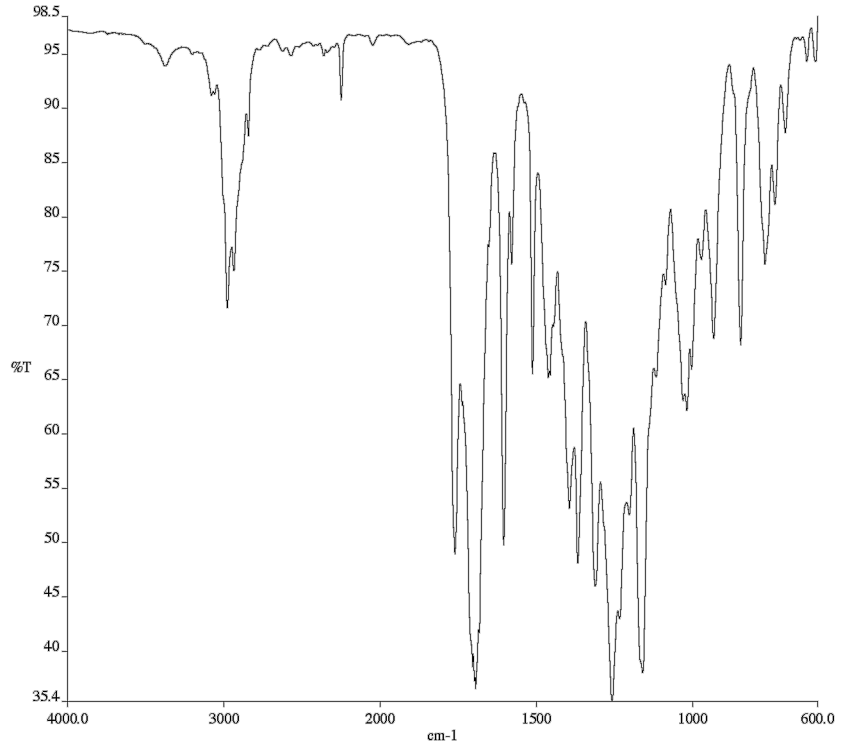
Infrared spectrum (Thin Film, NaCl) of compound **3i**.



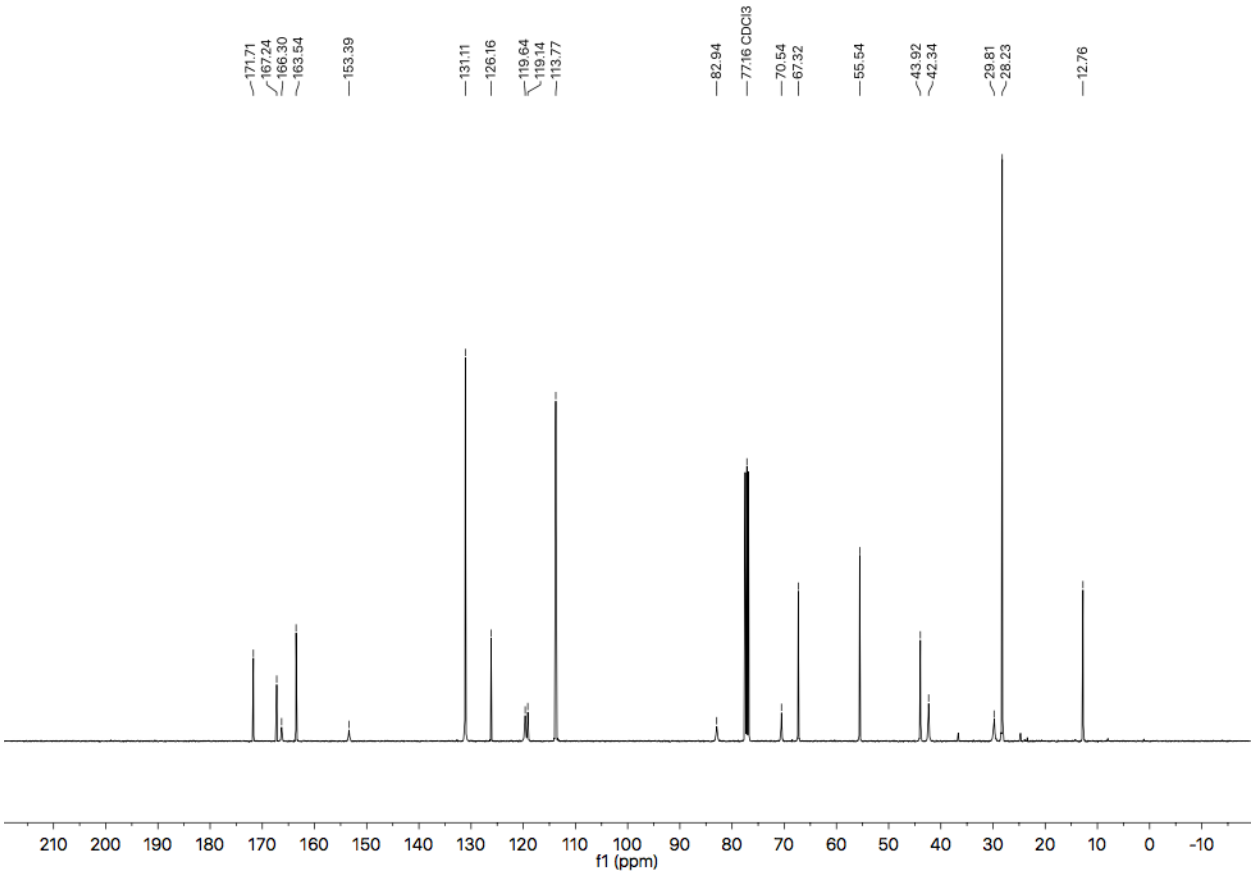
^{13}C NMR (126 MHz, $CDCl_3$) of compound **3i**.



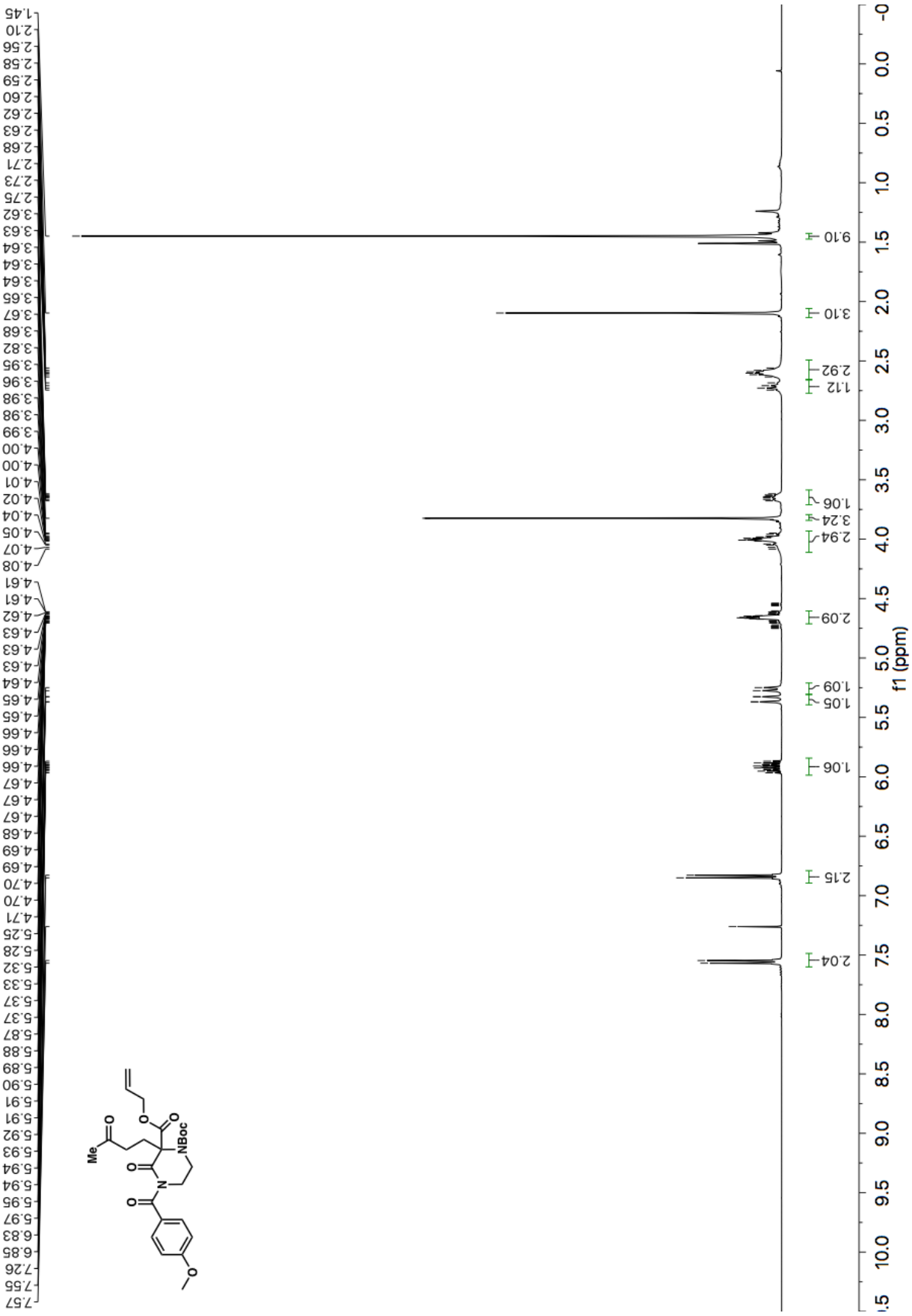
^{1}H NMR (400 MHz, $CDCl_3$) of compound **3j.**



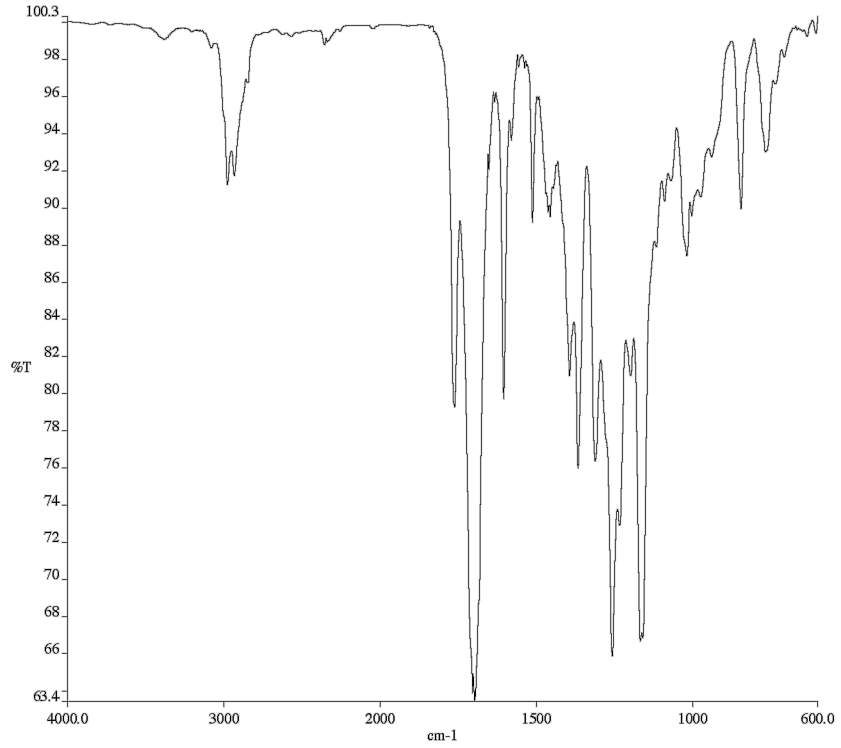
Infrared spectrum (Thin Film, NaCl) of compound **3j**.



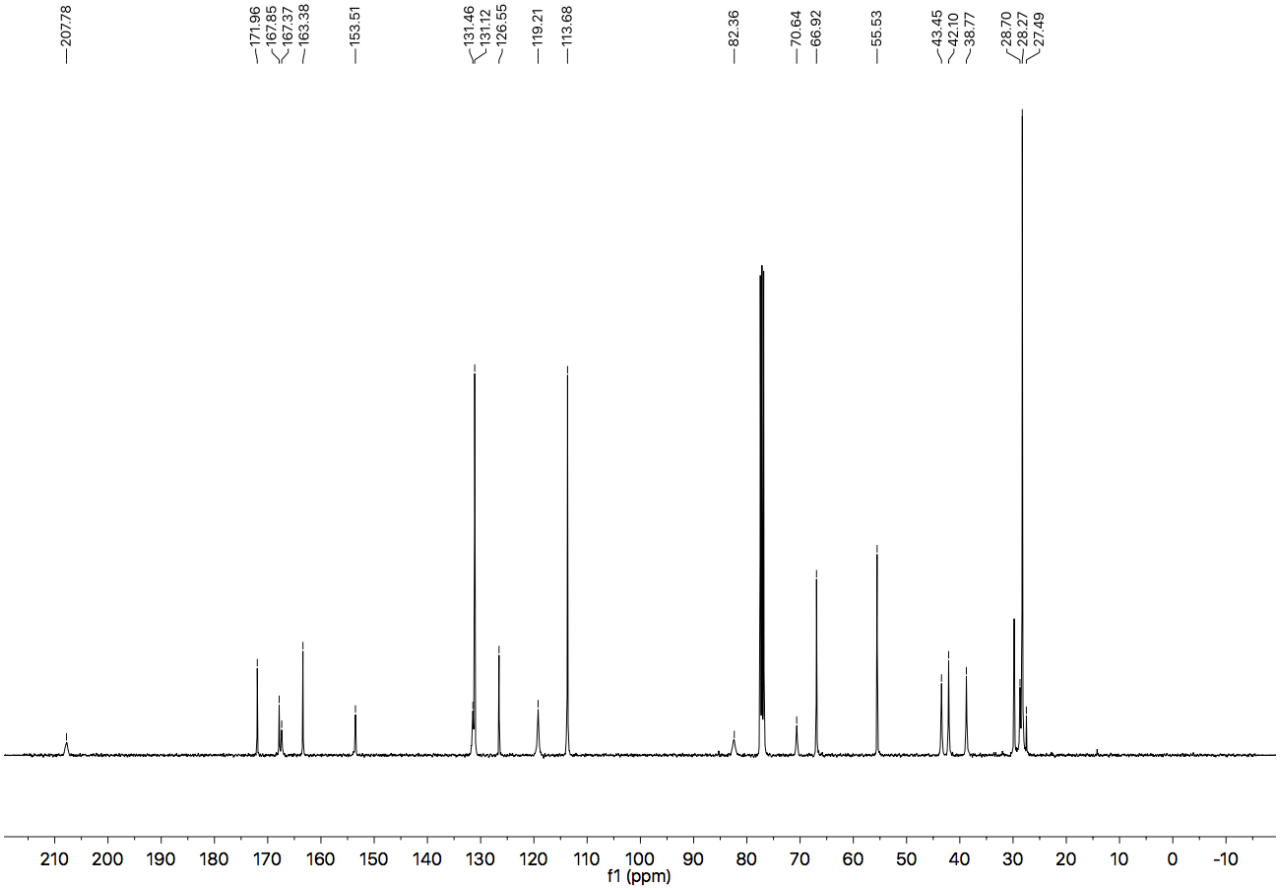
^{13}C NMR (101 MHz, $CDCl_3$) of compound **3j**.



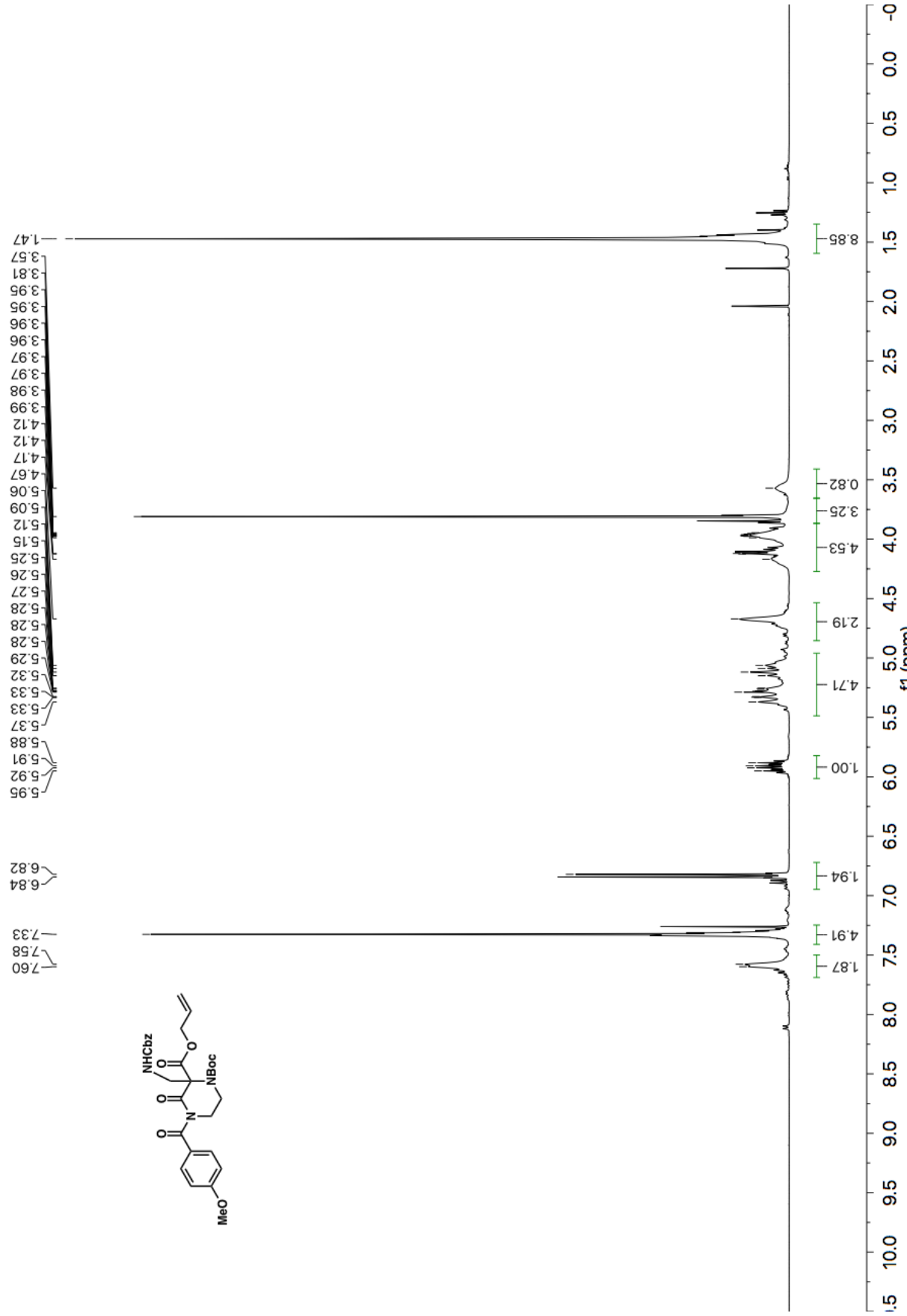
^{1}H NMR (400 MHz, $CDCl_3$) of compound **3k.**



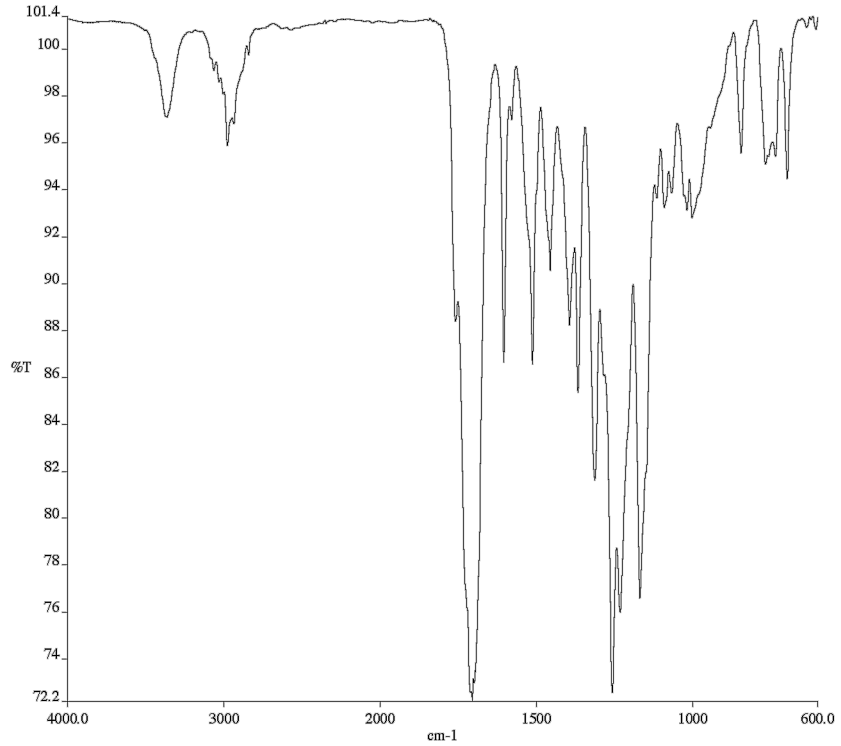
Infrared spectrum (Thin Film, NaCl) of compound **3k**.



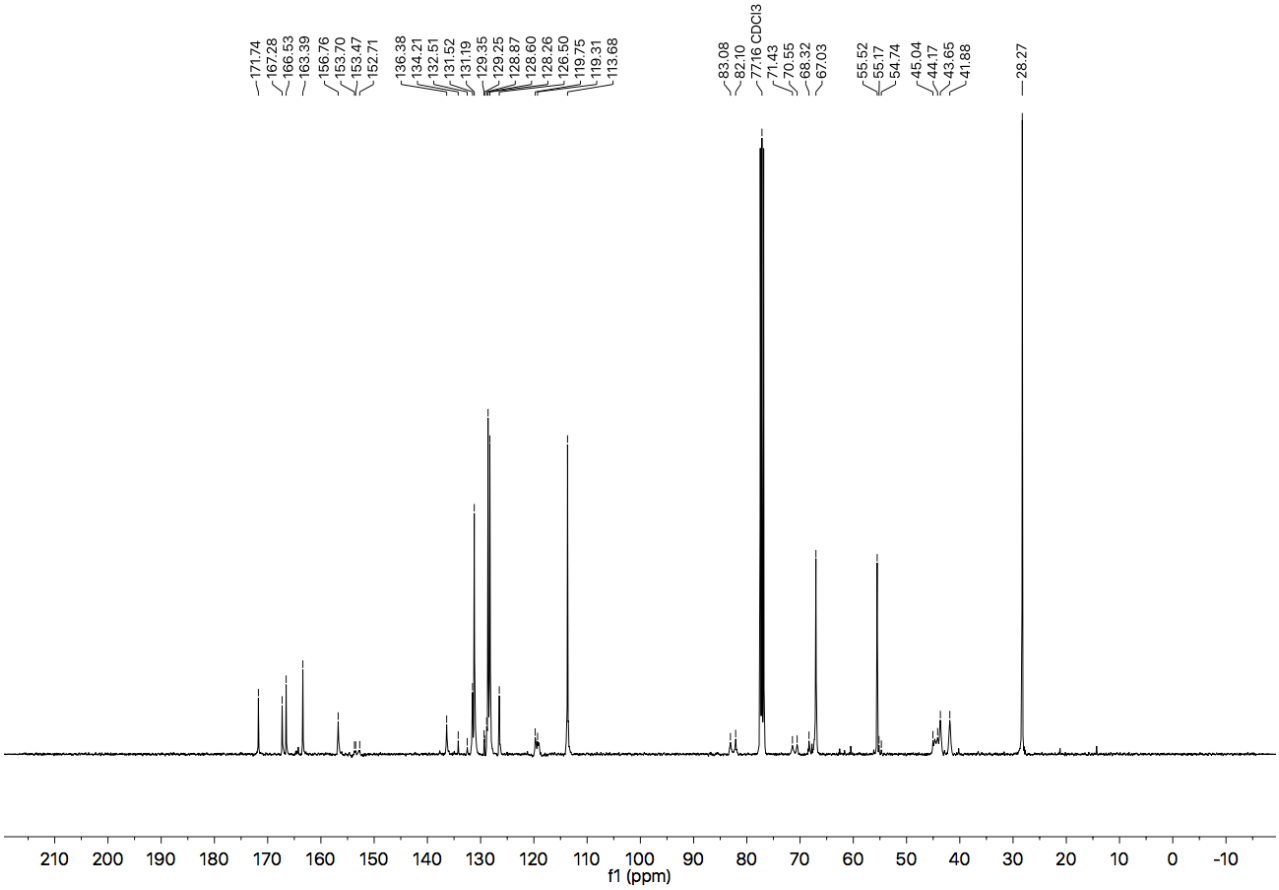
^{13}C NMR (101 MHz, $CDCl_3$) of compound **3k**.



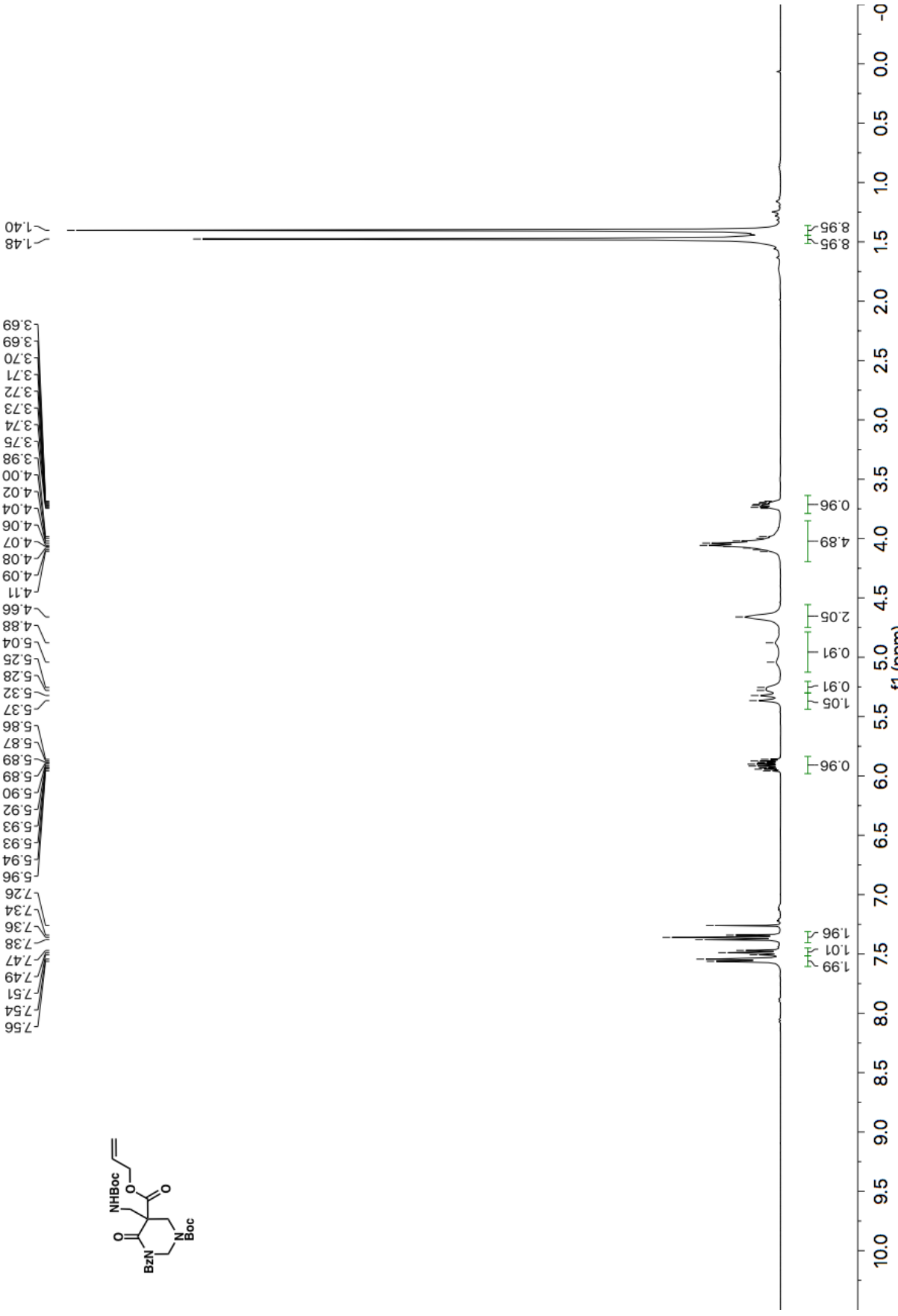
^{1}H NMR (400 MHz, $CDCl_3$) of compound **3l.**



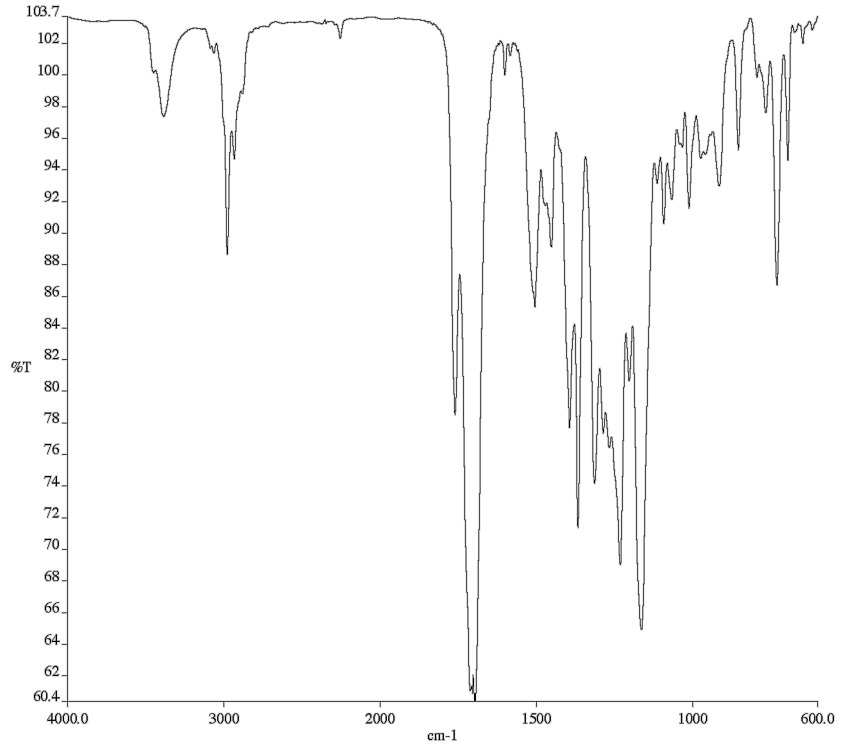
Infrared spectrum (Thin Film, NaCl) of compound **3l**.



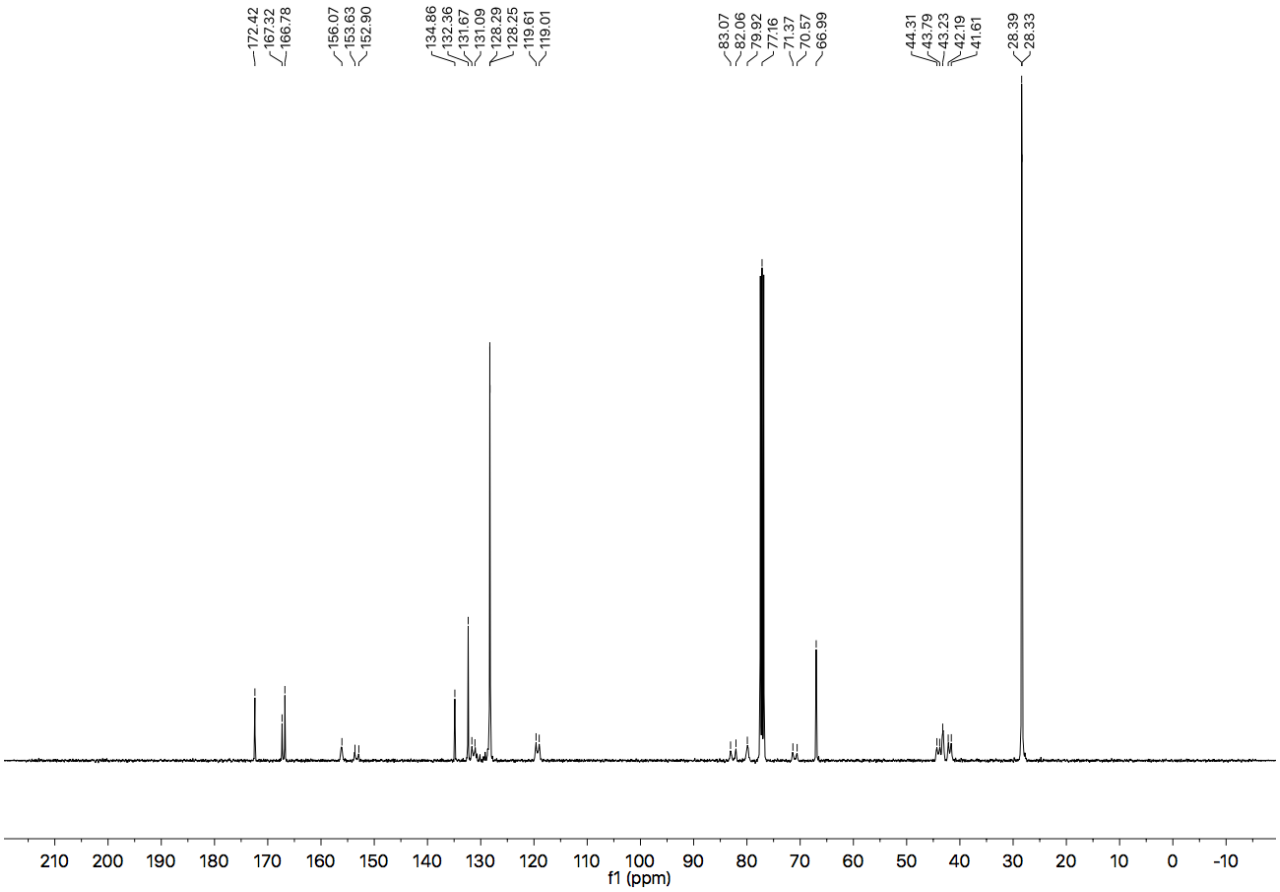
^{13}C NMR (101 MHz, $CDCl_3$) of compound **3l**.



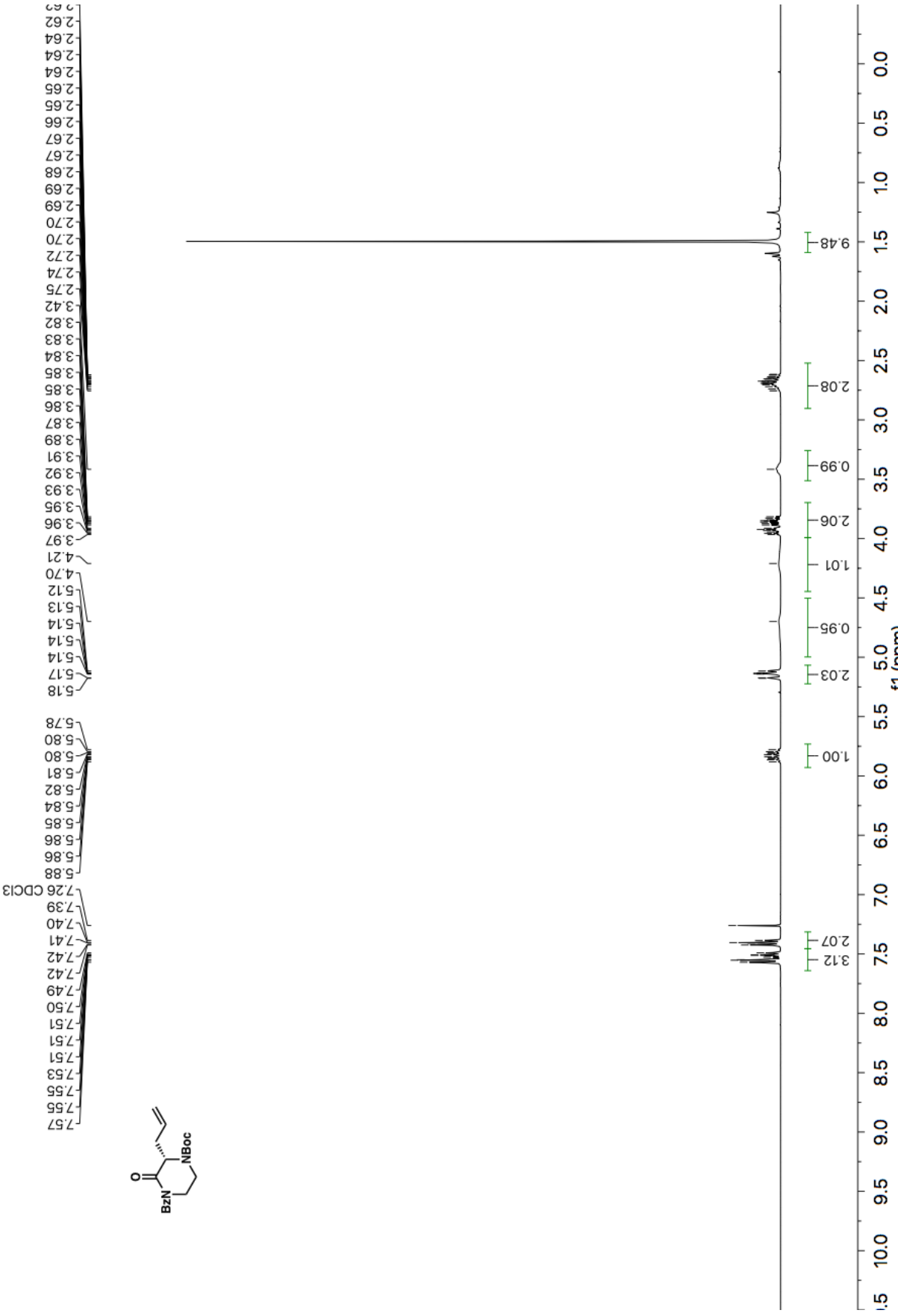
^{1}H NMR (400 MHz, $CDCl_3$) of compound **3m.**



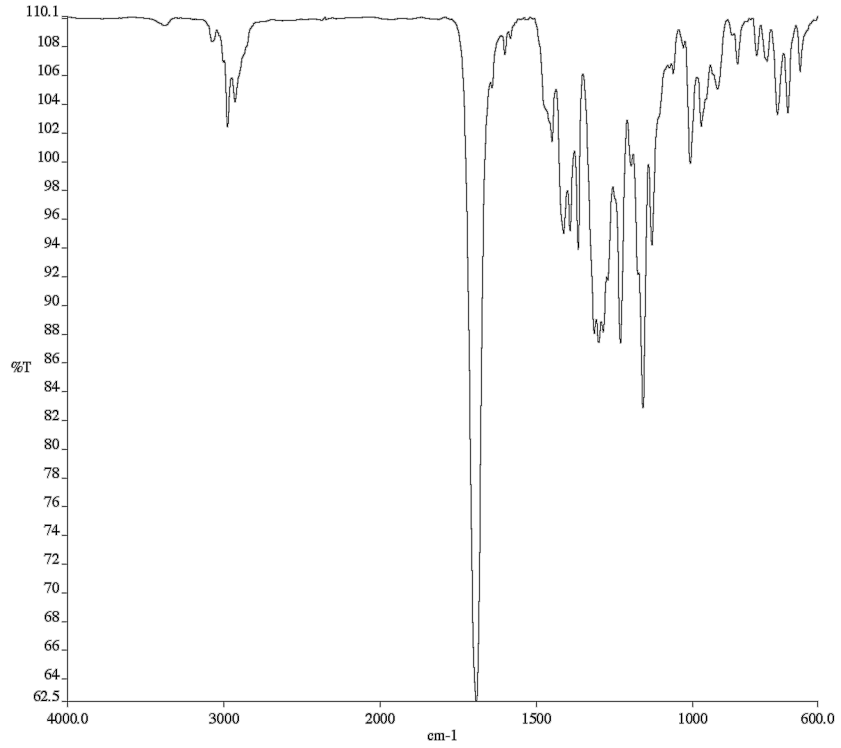
Infrared spectrum (Thin Film, NaCl) of compound **3m**.



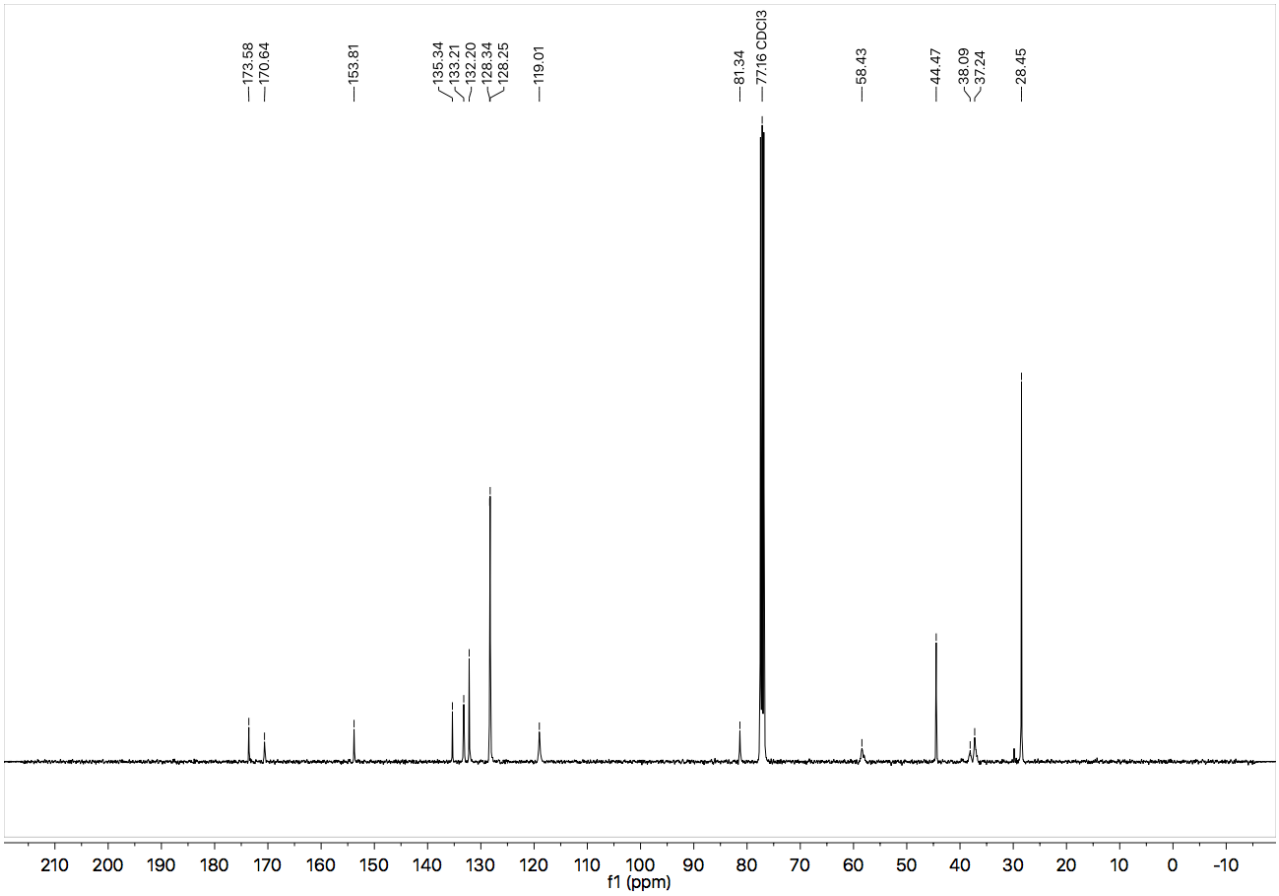
^{13}C NMR (101 MHz, $CDCl_3$) of compound **3m**.



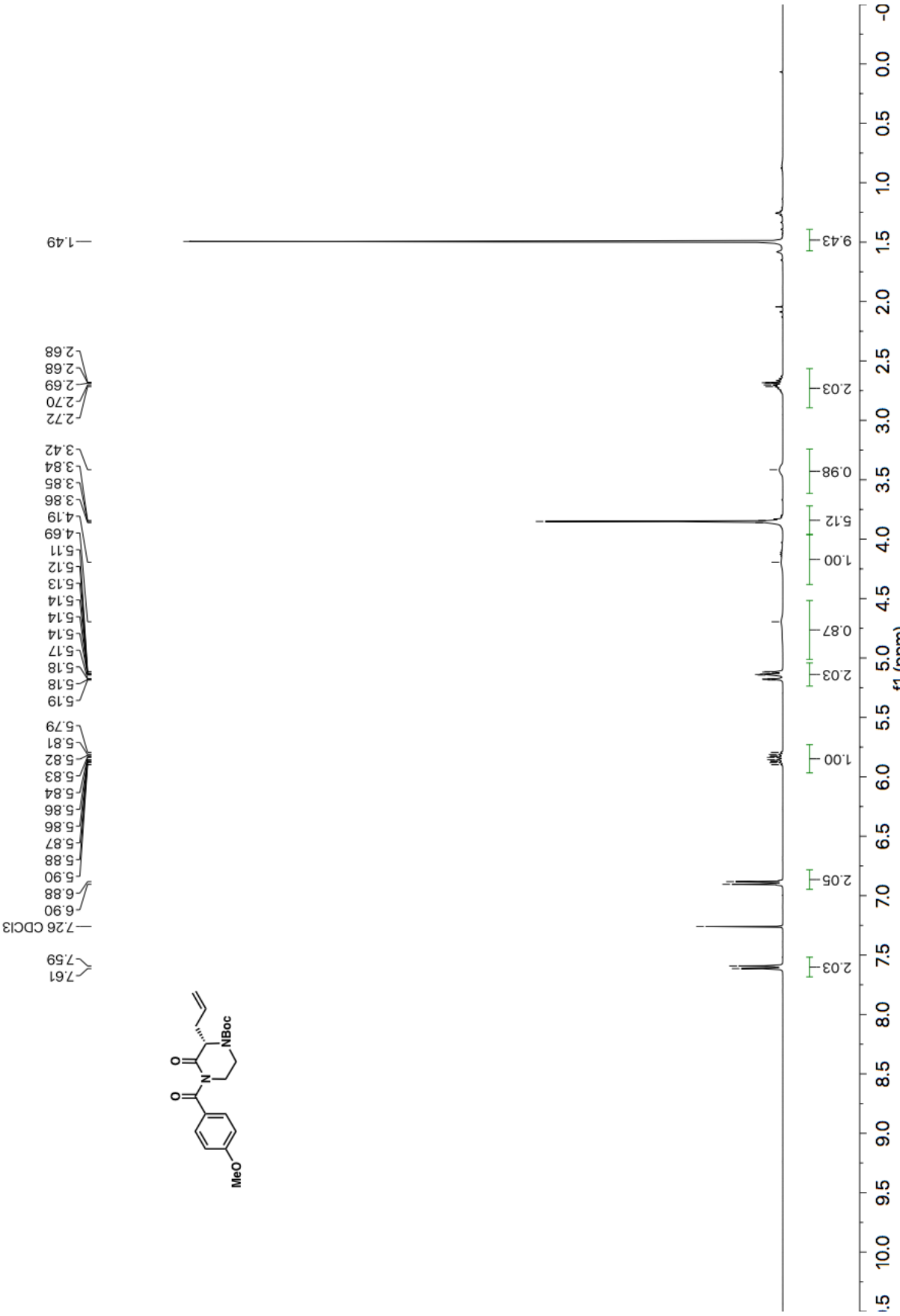
^{1}H NMR (400 MHz, $CDCl_3$) of compound **4a.**



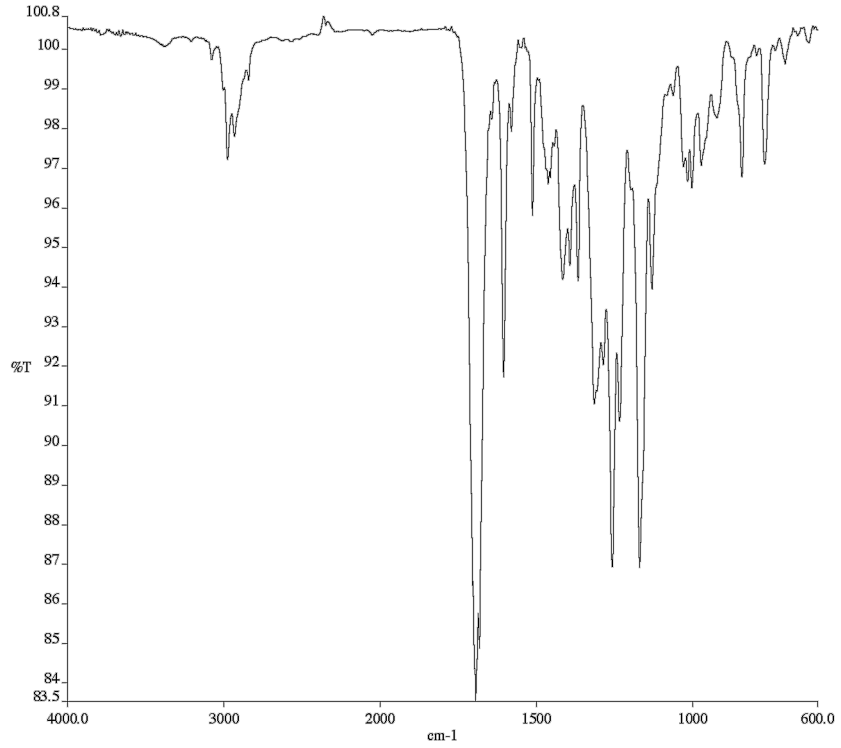
Infrared spectrum (Thin Film, NaCl) of compound **4a**.



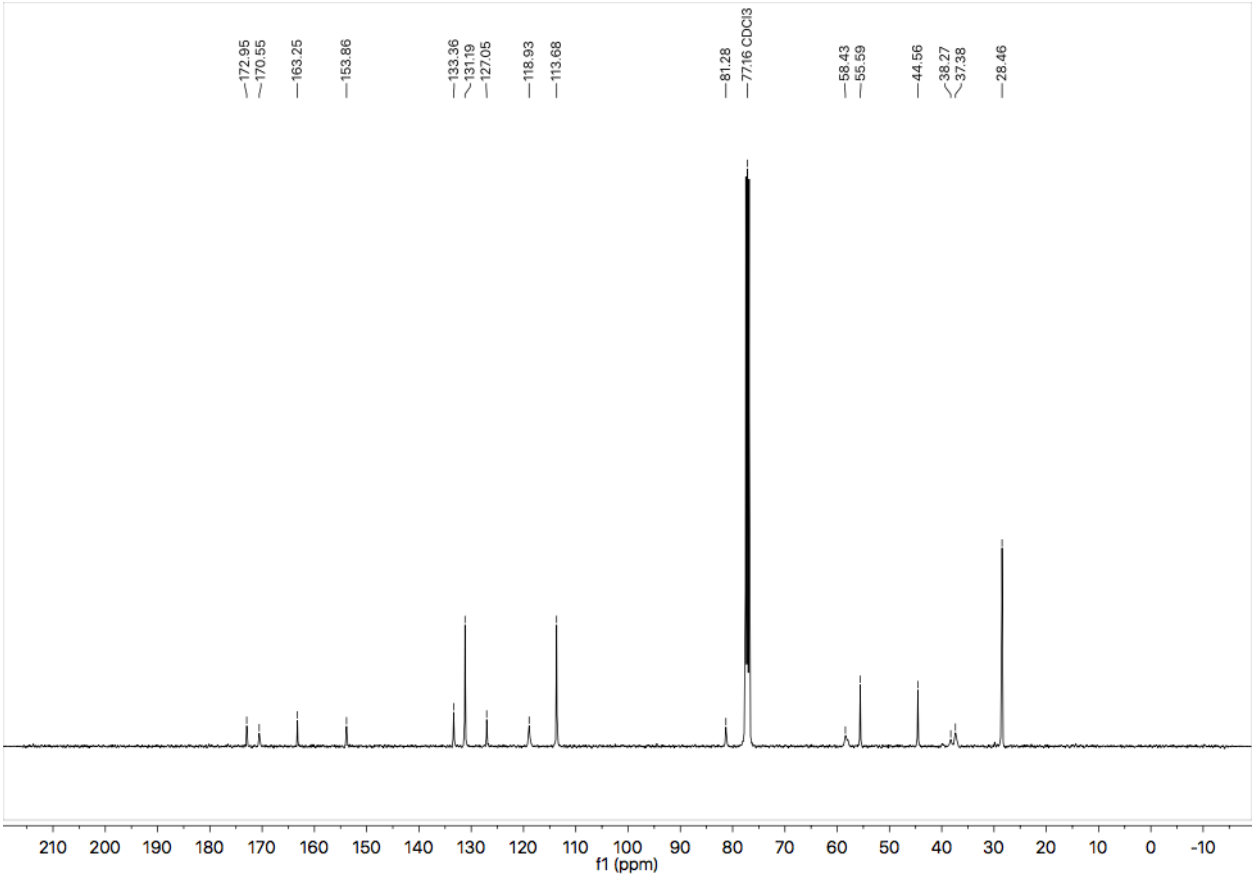
^{13}C NMR (101 MHz, $CDCl_3$) of compound **4a**.



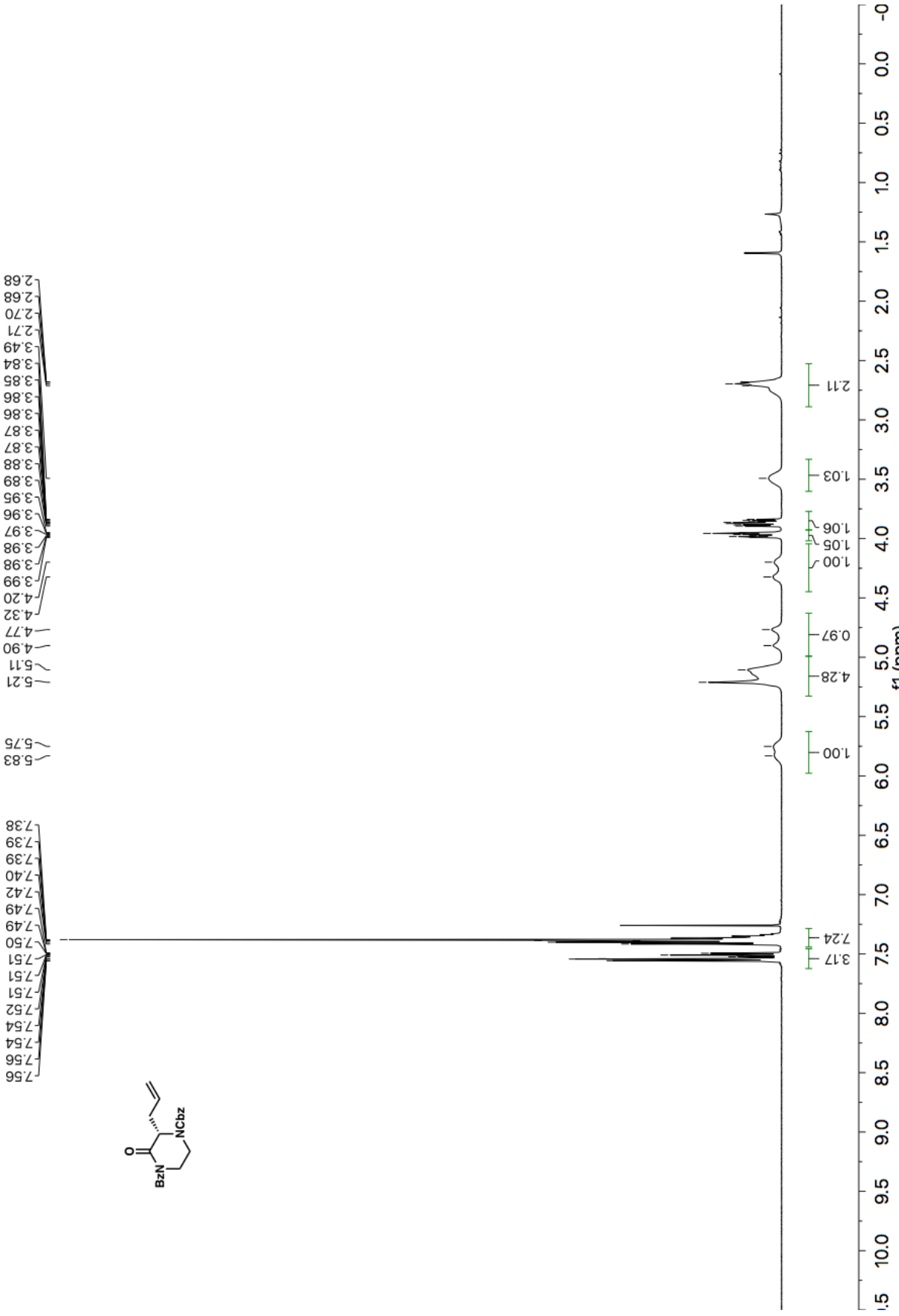
^{1}H NMR (400 MHz, $CDCl_3$) of compound **4b.**



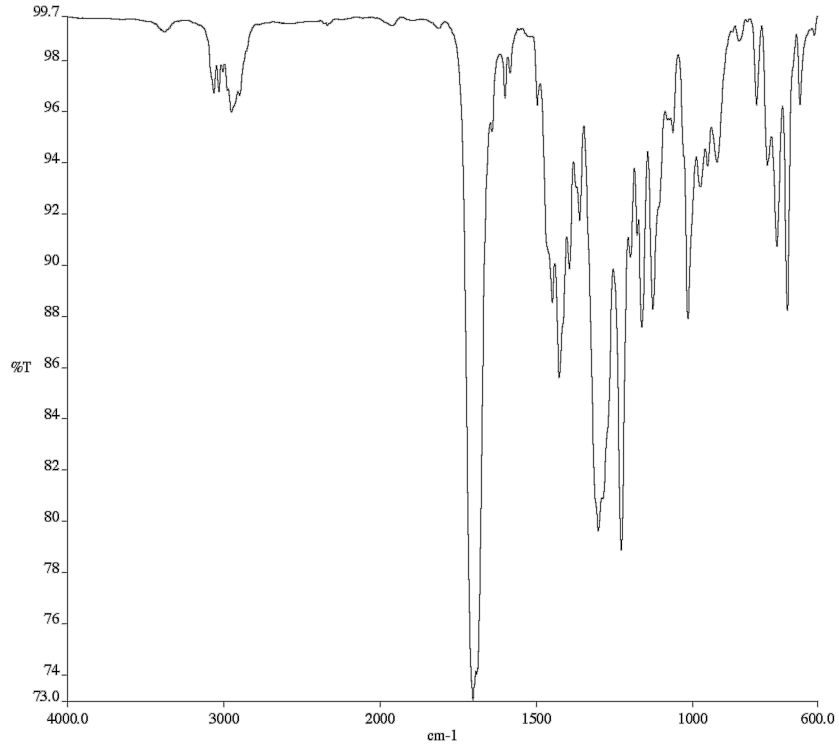
Infrared spectrum (Thin Film, NaCl) of compound **4b**.



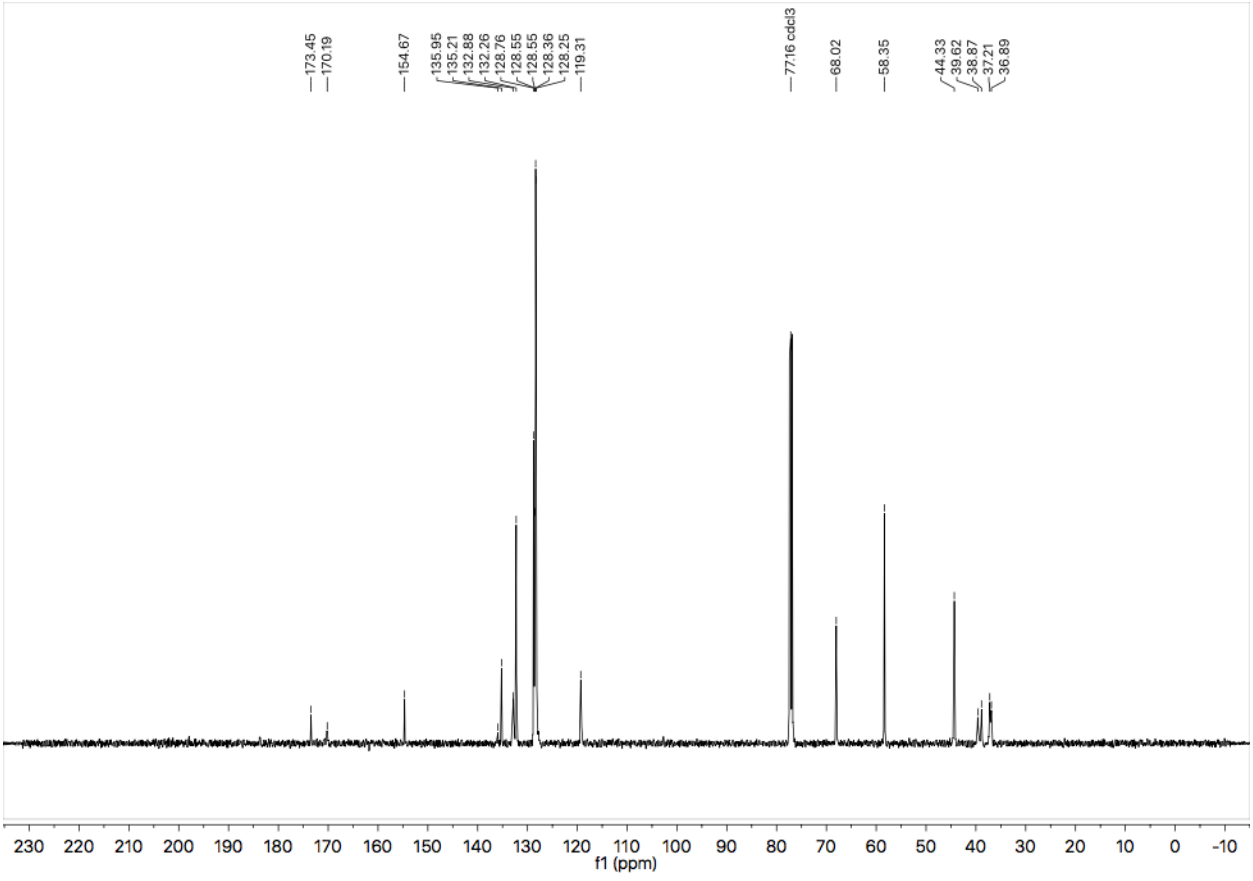
^{13}C NMR (101 MHz, $CDCl_3$) of compound **4b**.



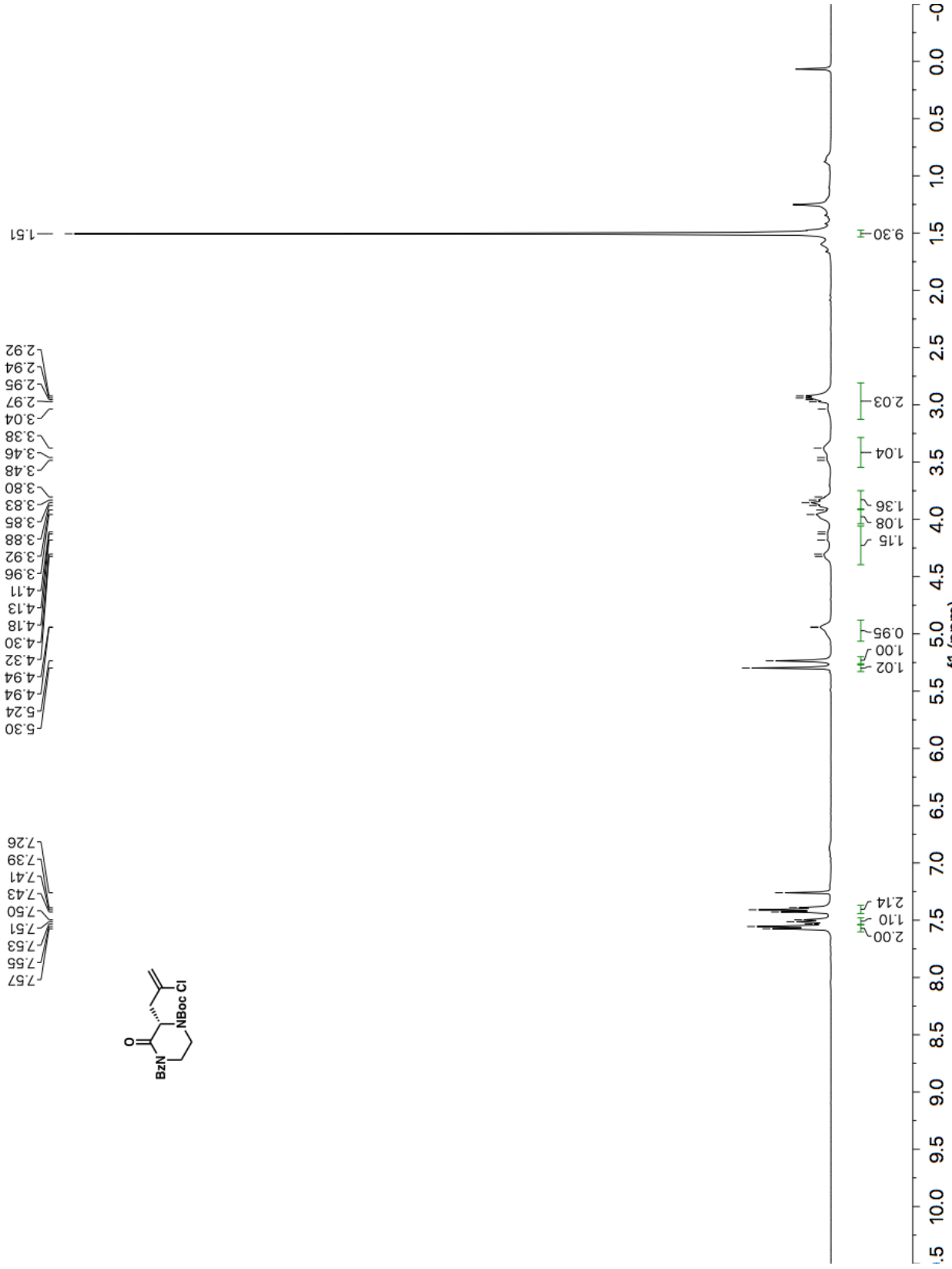
^{1}H NMR (400 MHz, $CDCl_3$) of compound **4c.**



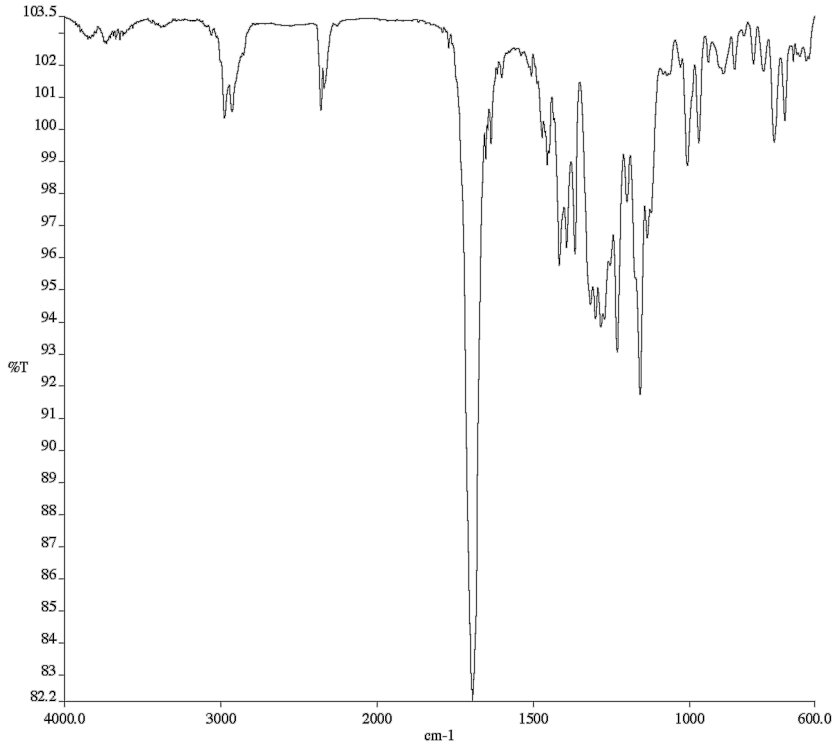
Infrared spectrum (Thin Film, NaCl) of compound **4c**.



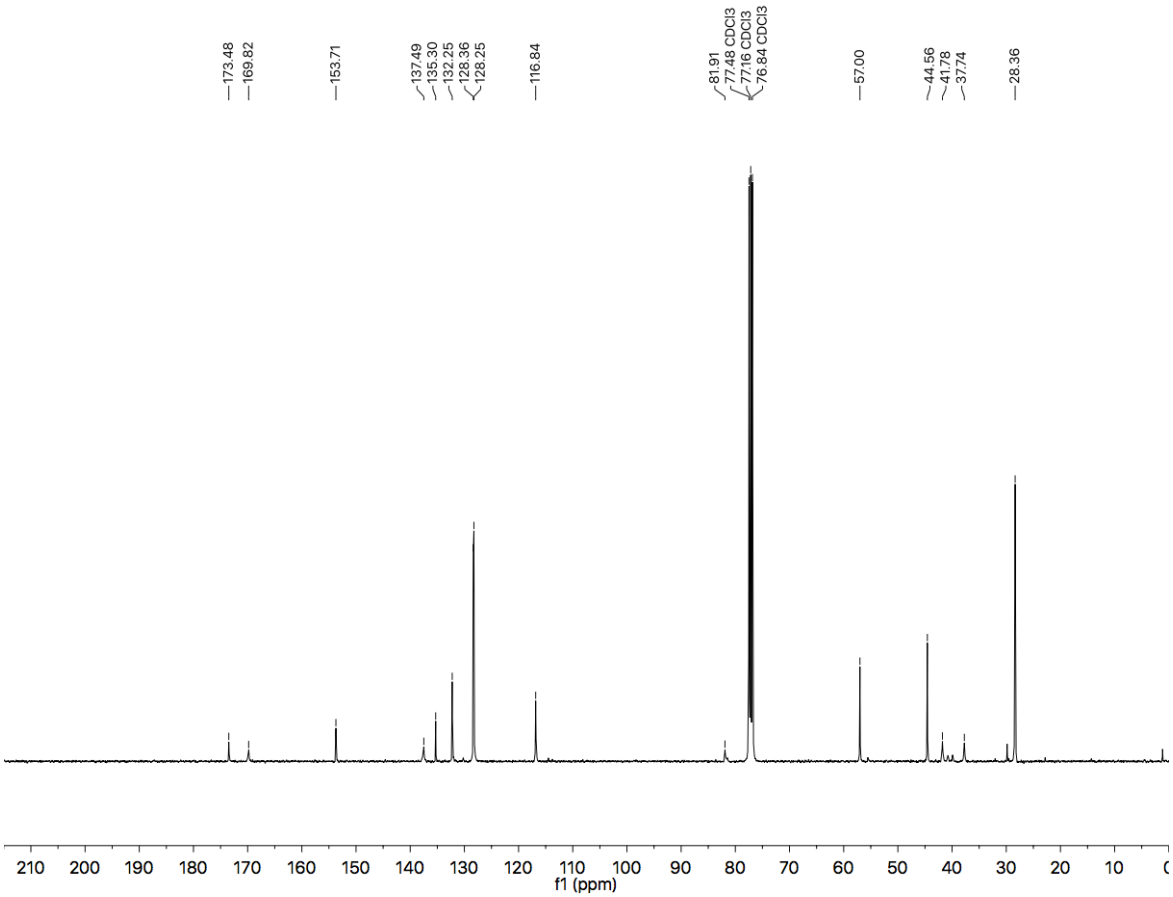
^{13}C NMR (101 MHz, $CDCl_3$) of compound **4c**.



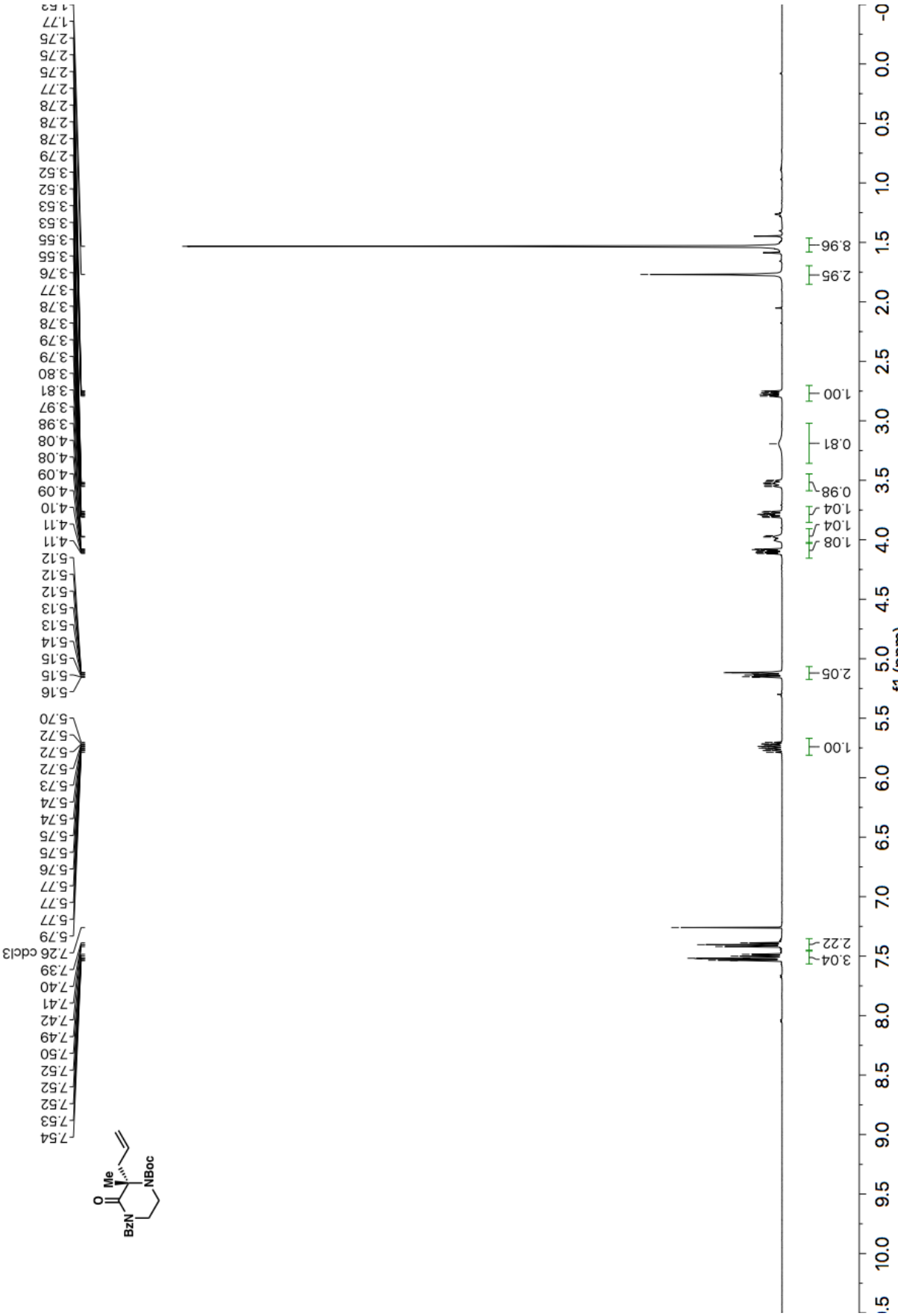
^{1}H NMR (500 MHz, $CDCl_3$) of compound **4d.**



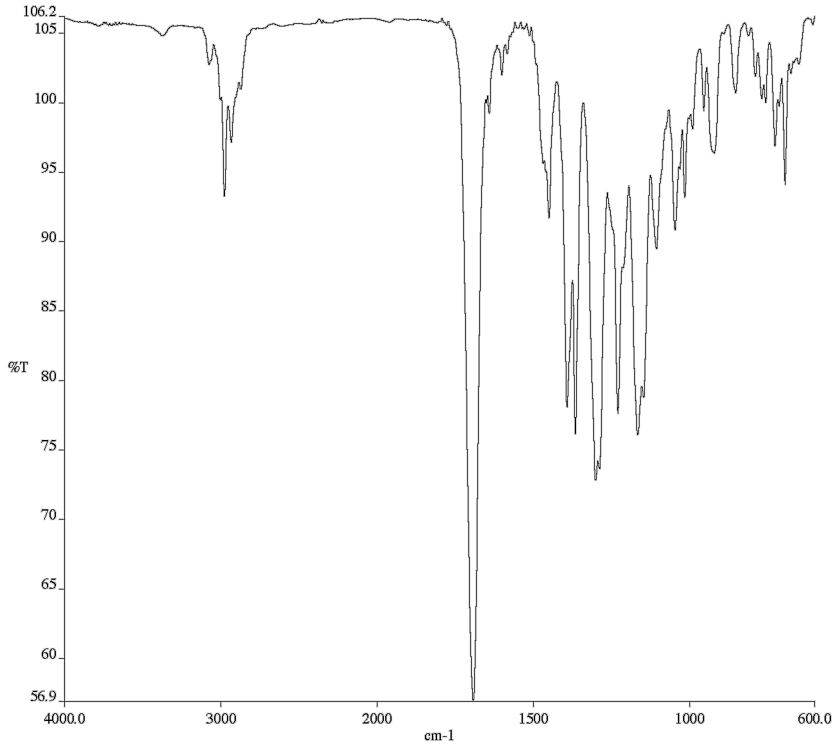
Infrared spectrum (Thin Film, NaCl) of compound **4d**.



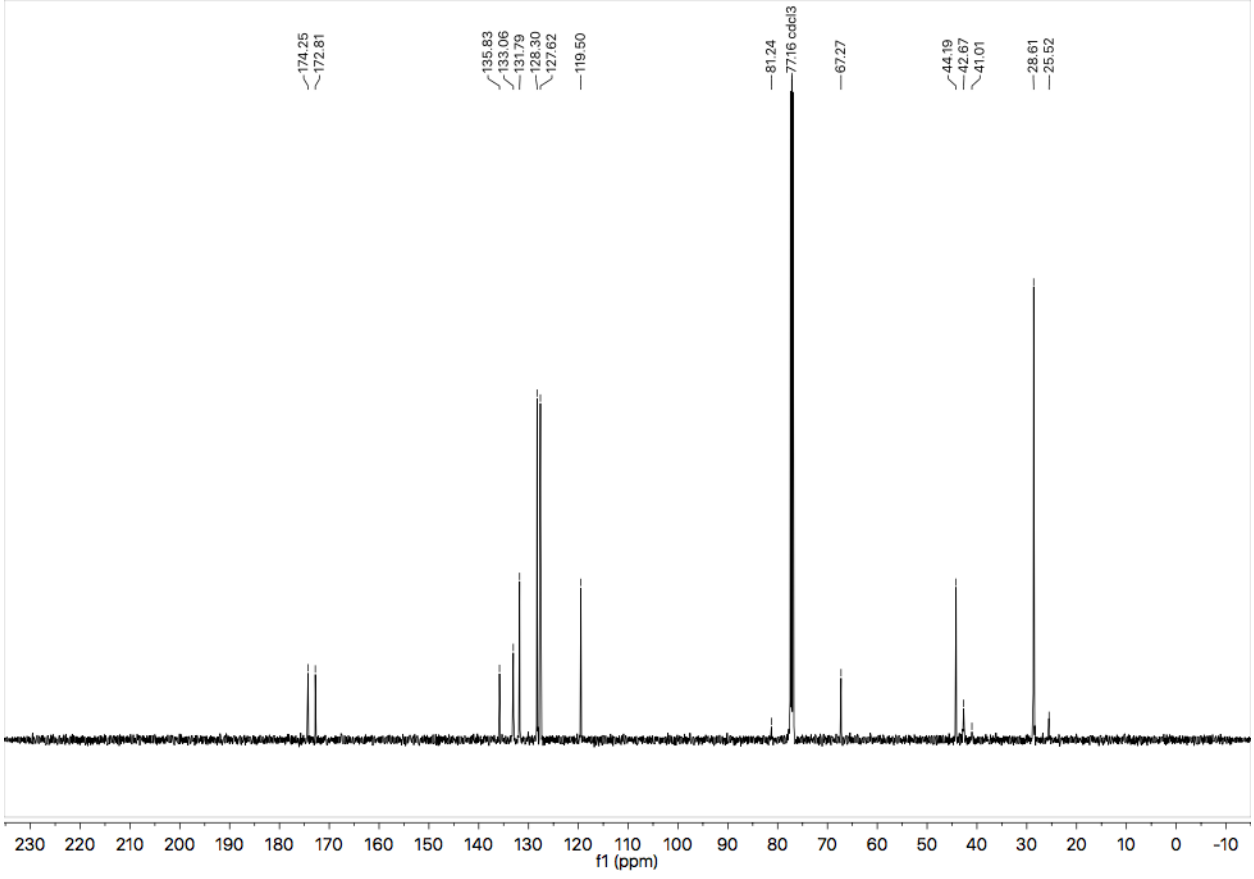
^{13}C NMR (126 MHz, $CDCl_3$) of compound **4d**.



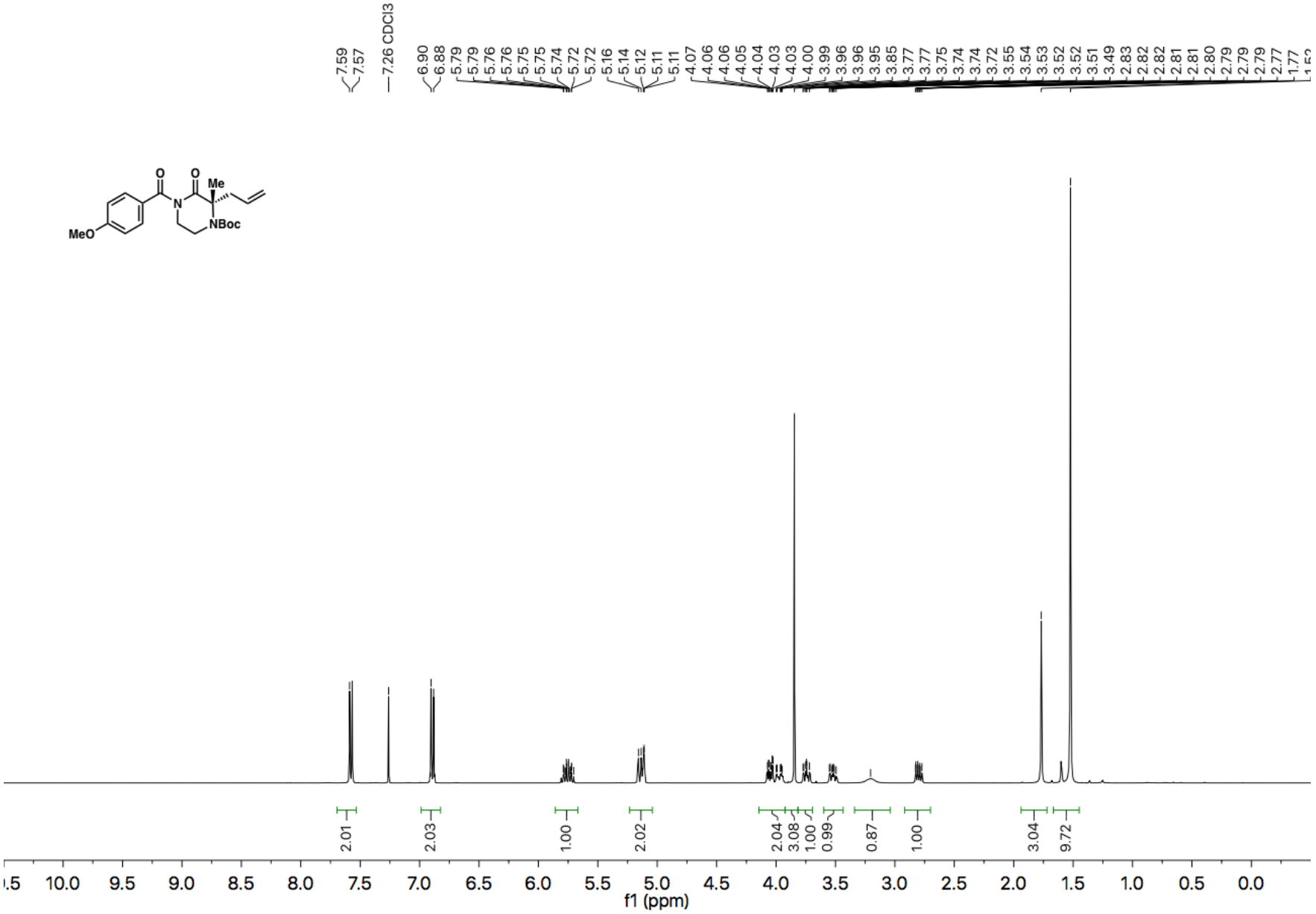
^{1}H NMR (500 MHz, $CDCl_3$) of compound **4e.**



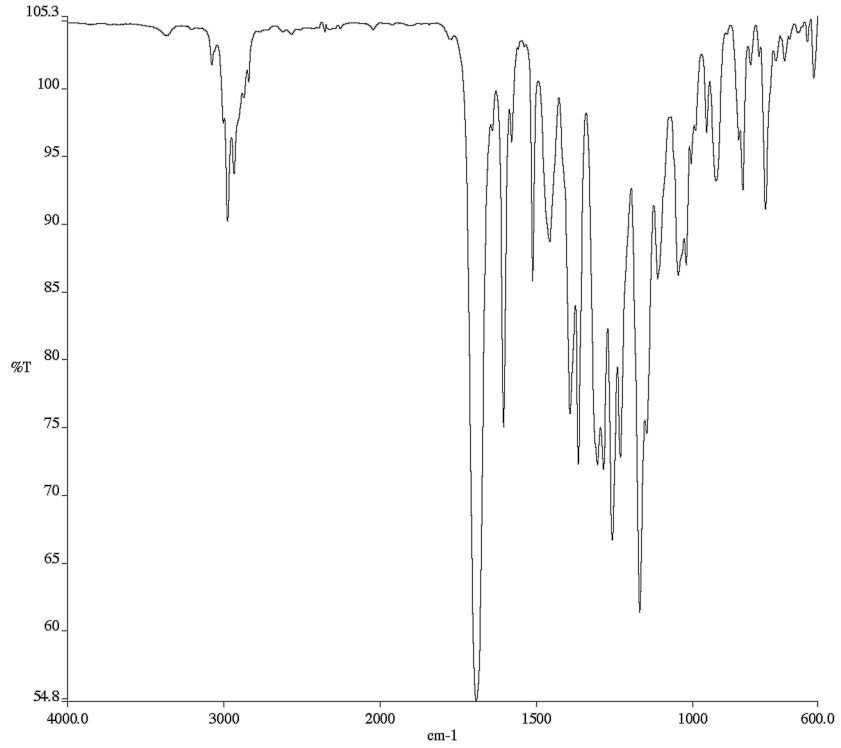
Infrared spectrum (Thin Film, NaCl) of compound **4e**.



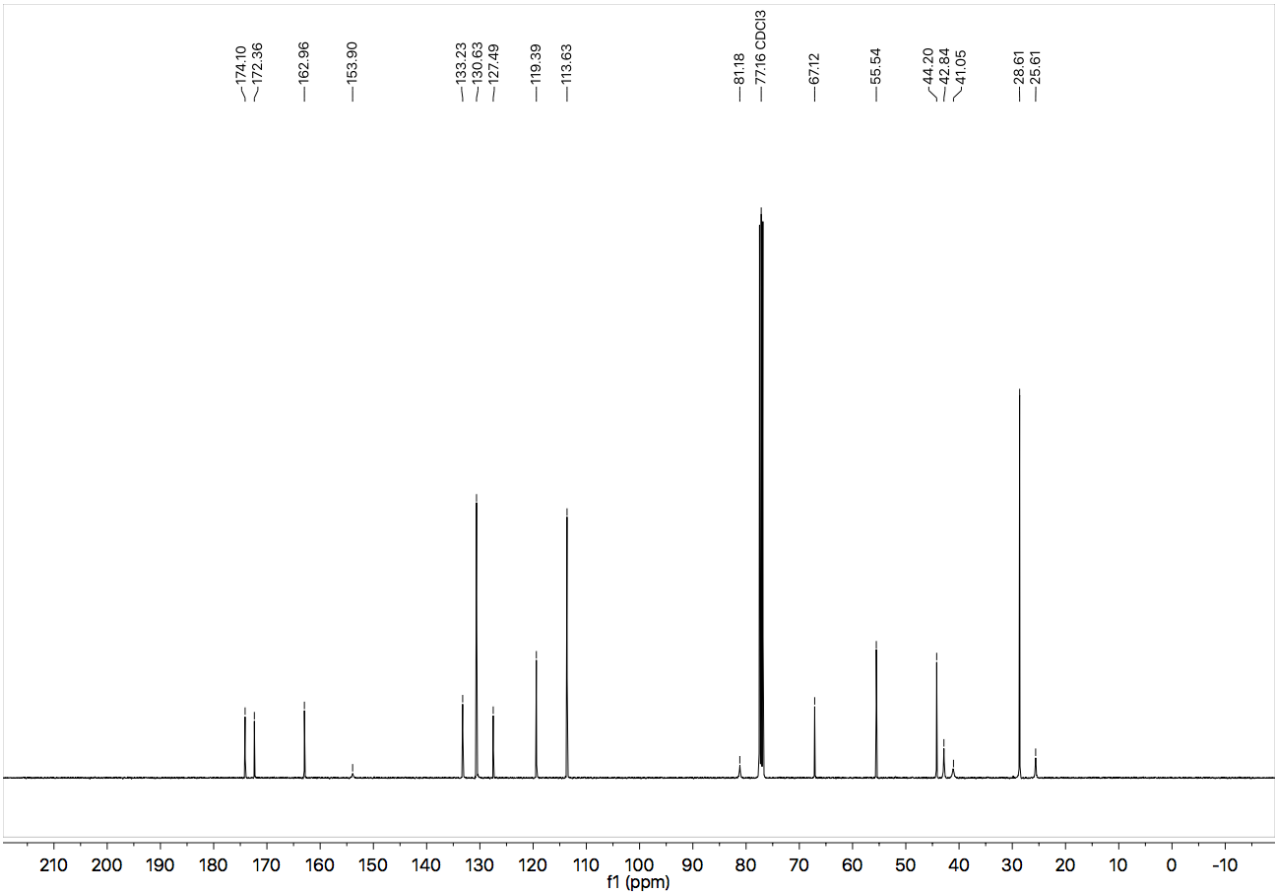
^{13}C NMR (126 MHz, $CDCl_3$) of compound **4e**.



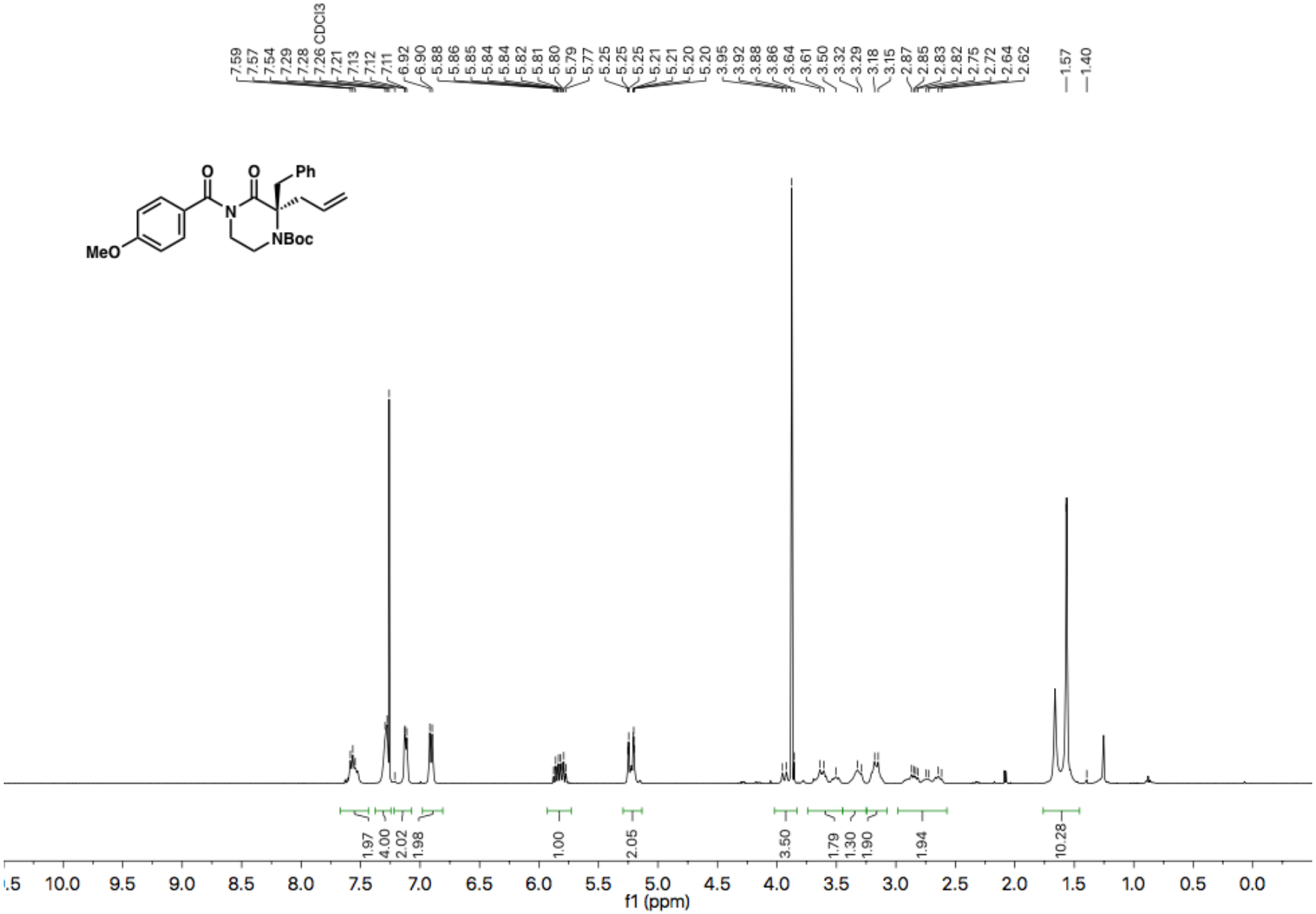
^{1}H NMR (400 MHz, $CDCl_3$) of compound **4f.**



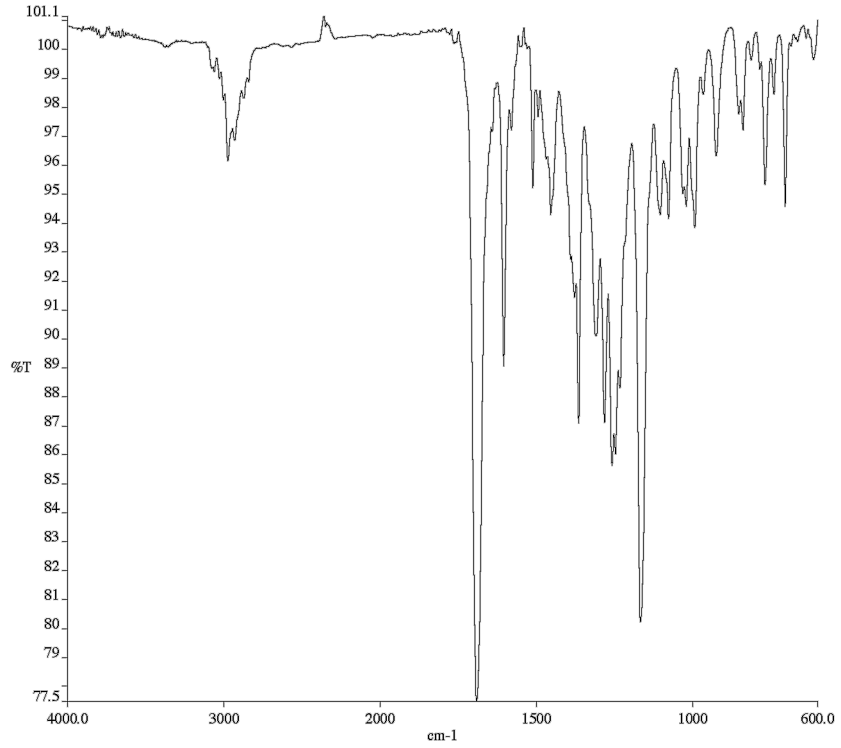
Infrared spectrum (Thin Film, NaCl) of compound **4f**.



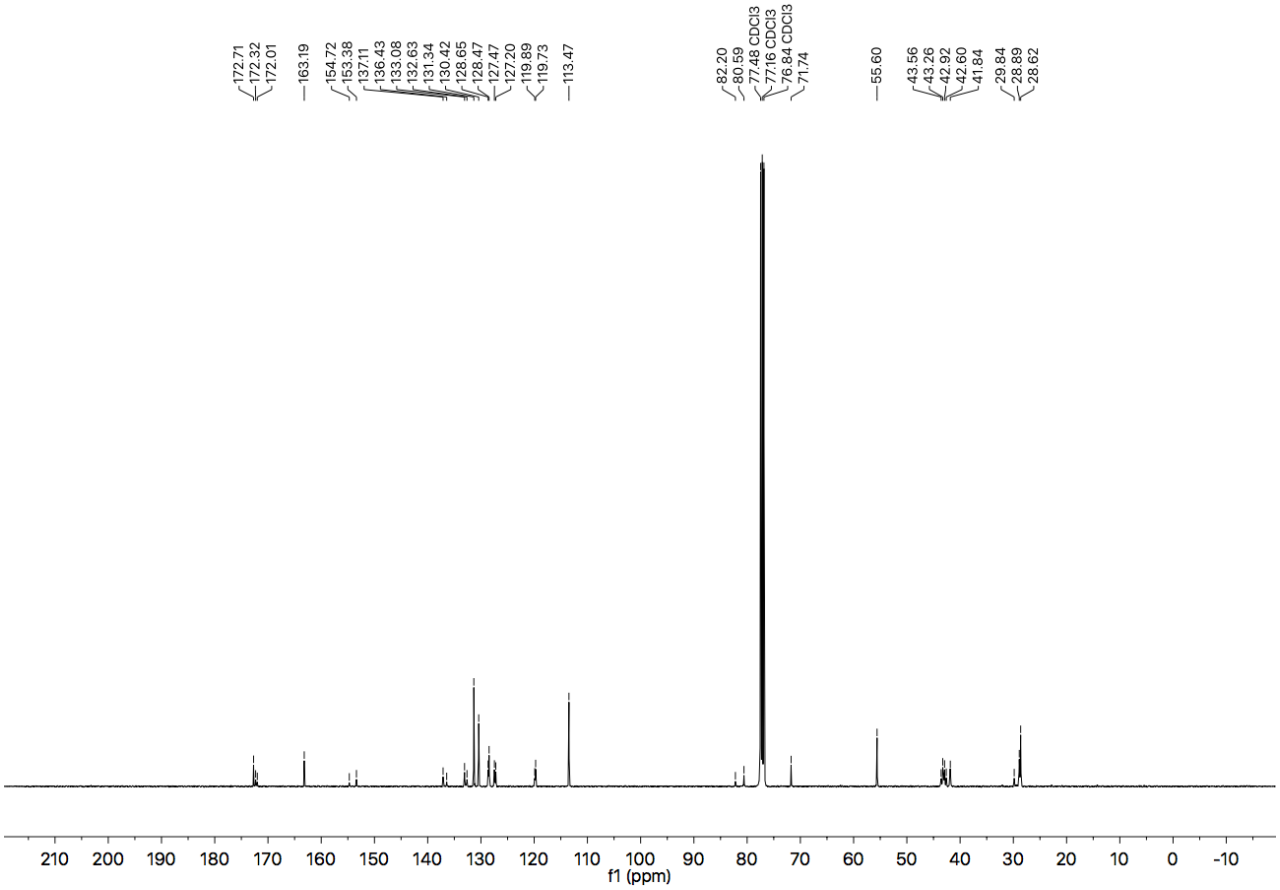
^{13}C NMR (101 MHz, $CDCl_3$) of compound **4f**.



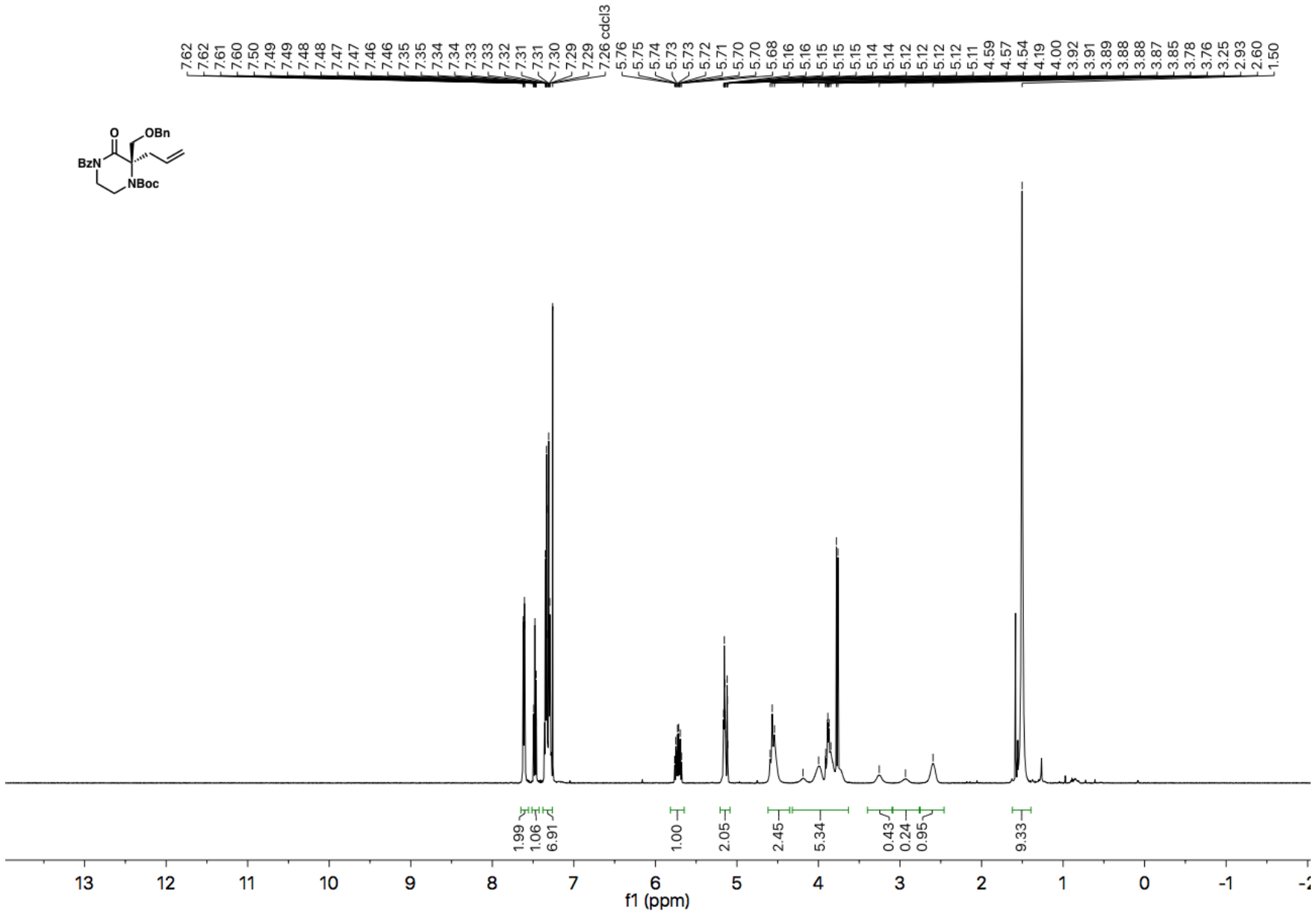
^{1}H NMR (400 MHz, $CDCl_3$) of compound **4h.**



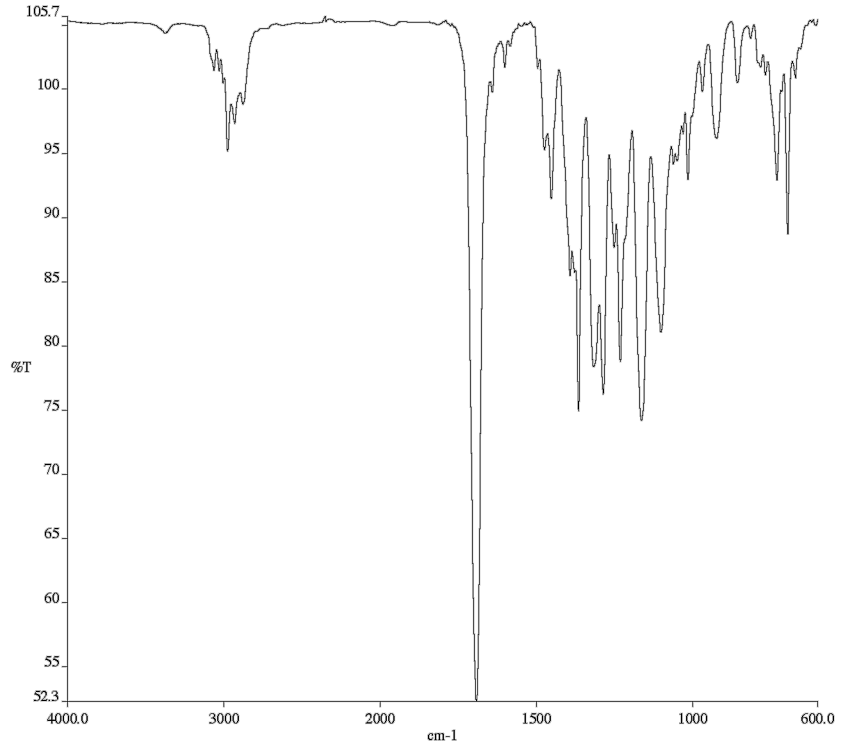
Infrared spectrum (Thin Film, NaCl) of compound **4h**.



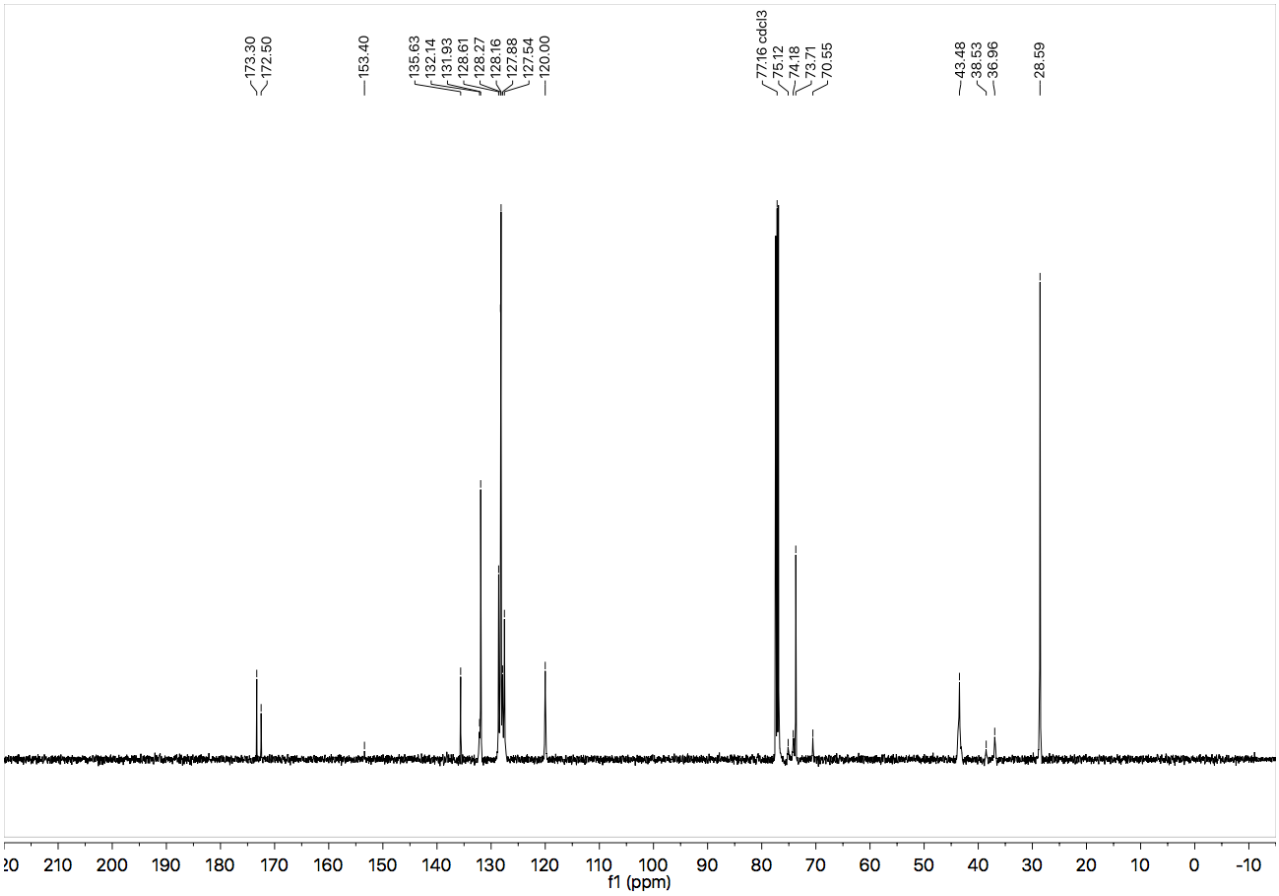
^{13}C NMR (101 MHz, $CDCl_3$) of compound **4h**.



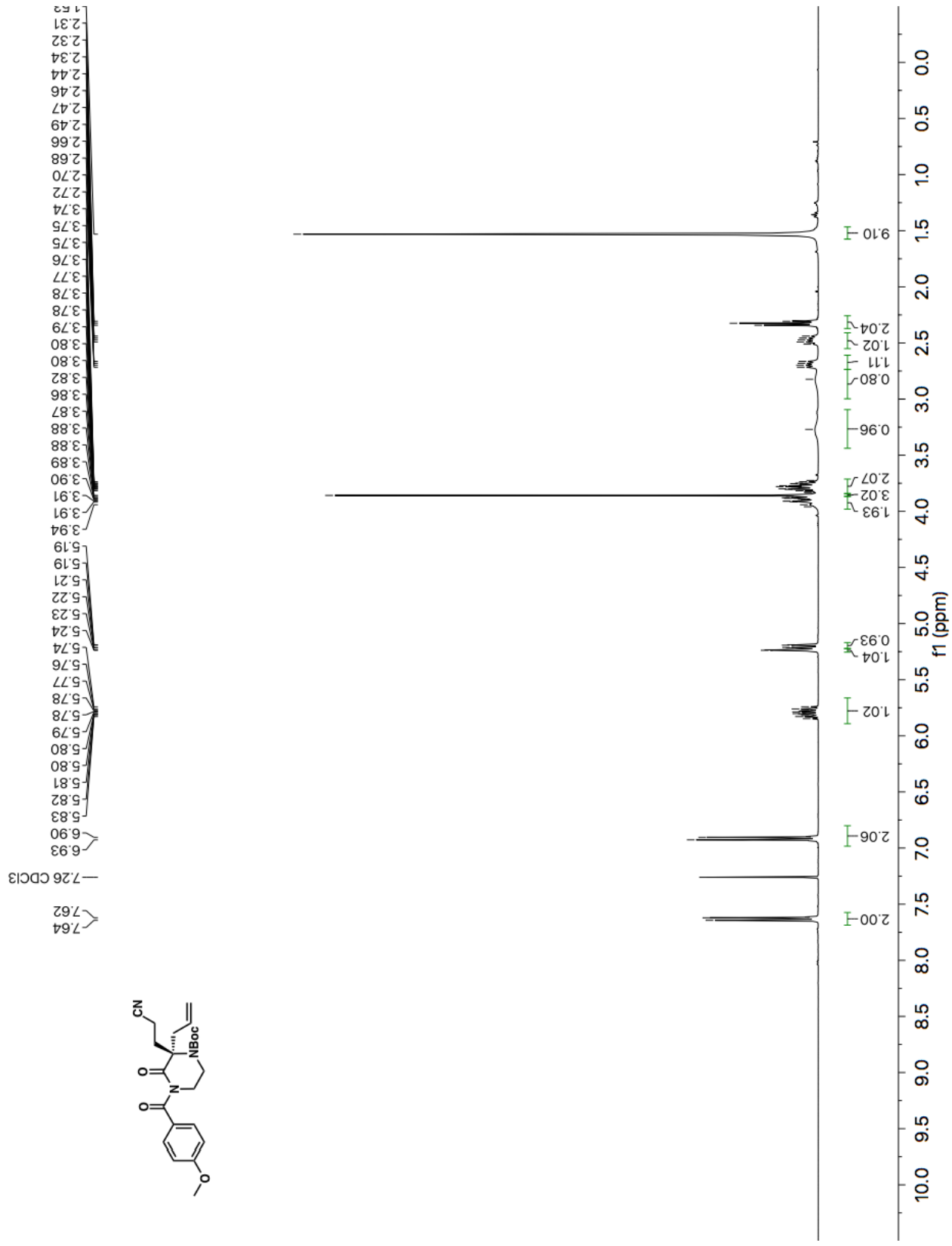
^{1}H NMR (500 MHz, $CDCl_3$) of compound **4i.**



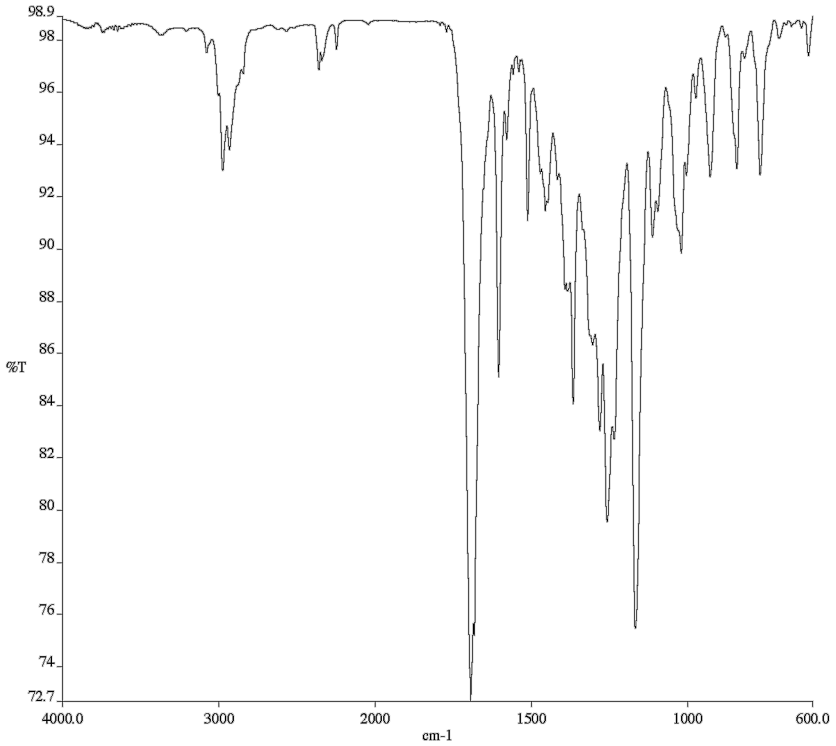
Infrared spectrum (Thin Film, NaCl) of compound **4i**.



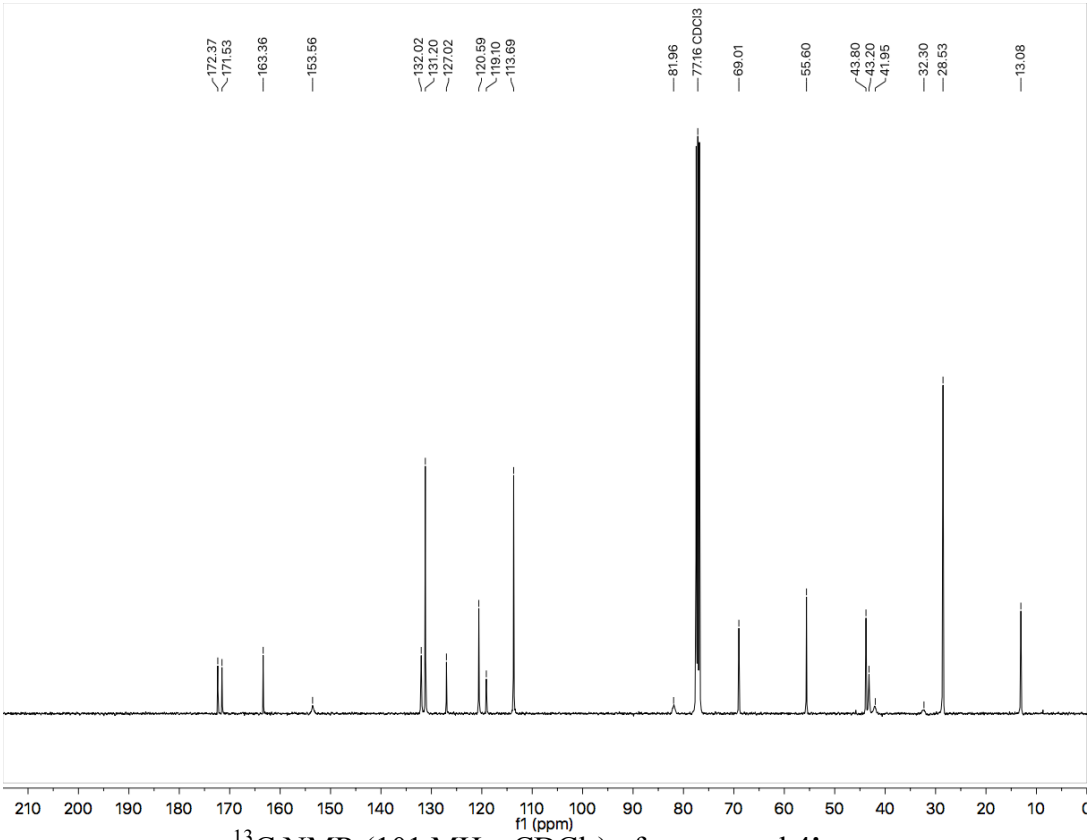
^{13}C NMR (126 MHz, $CDCl_3$) of compound **4i**.



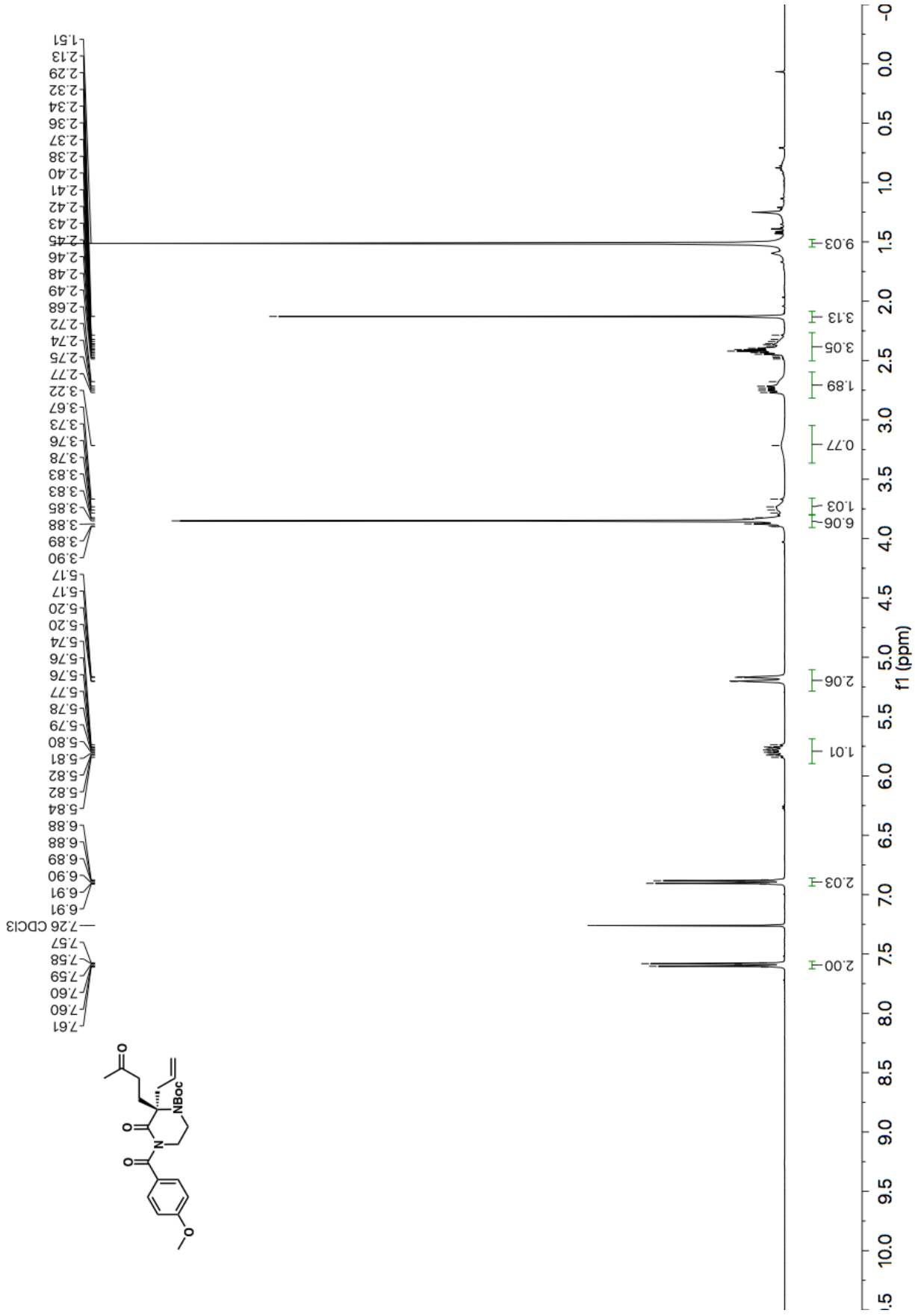
^{1}H NMR (400 MHz, $CDCl_3$) of compound **4j.**



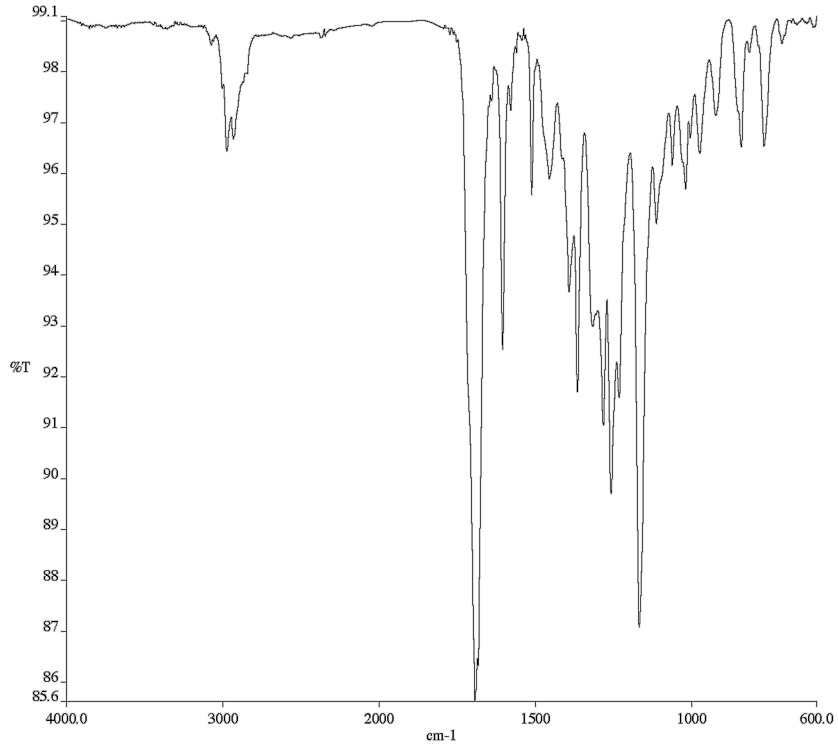
Infrared spectrum (Thin Film, NaCl) of compound **4j**.



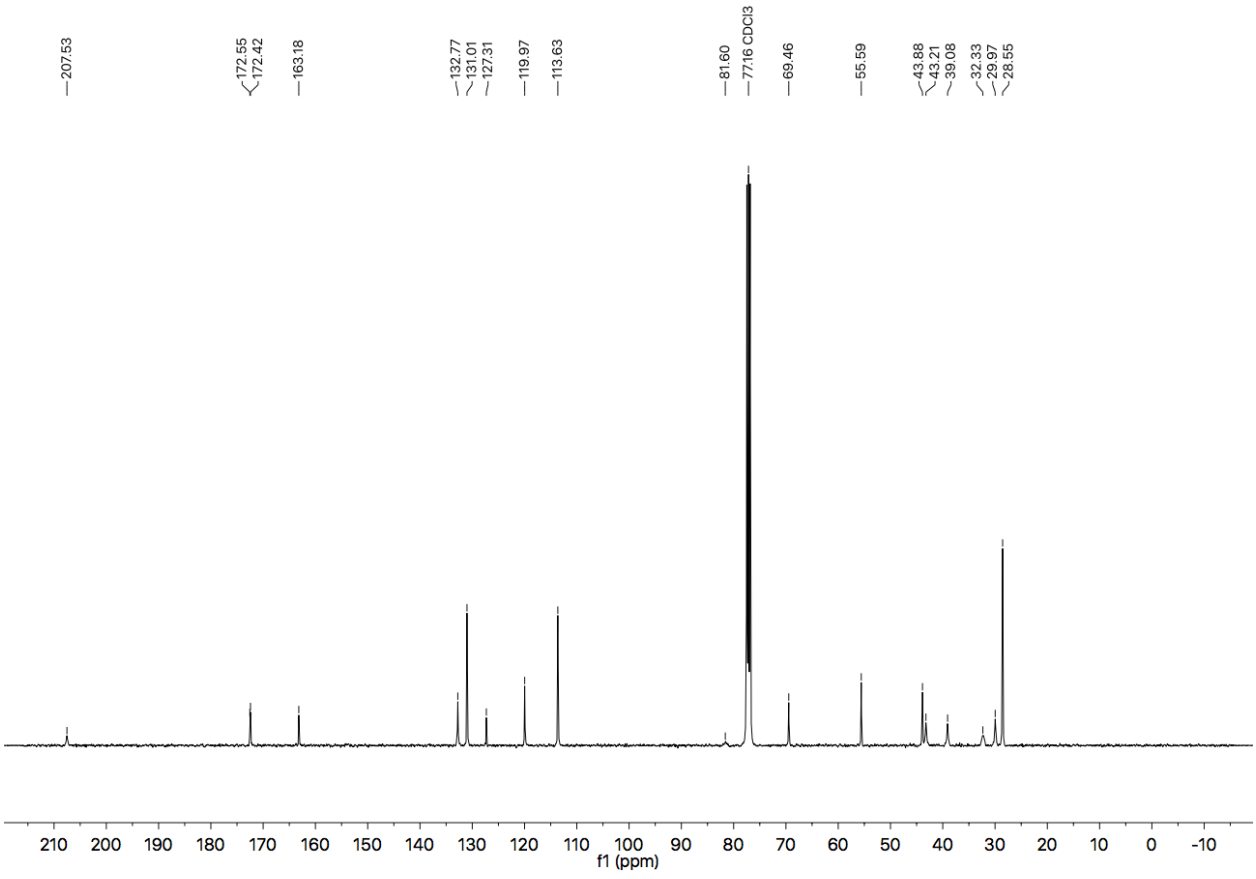
^{13}C NMR (101 MHz, $CDCl_3$) of compound **4j**.



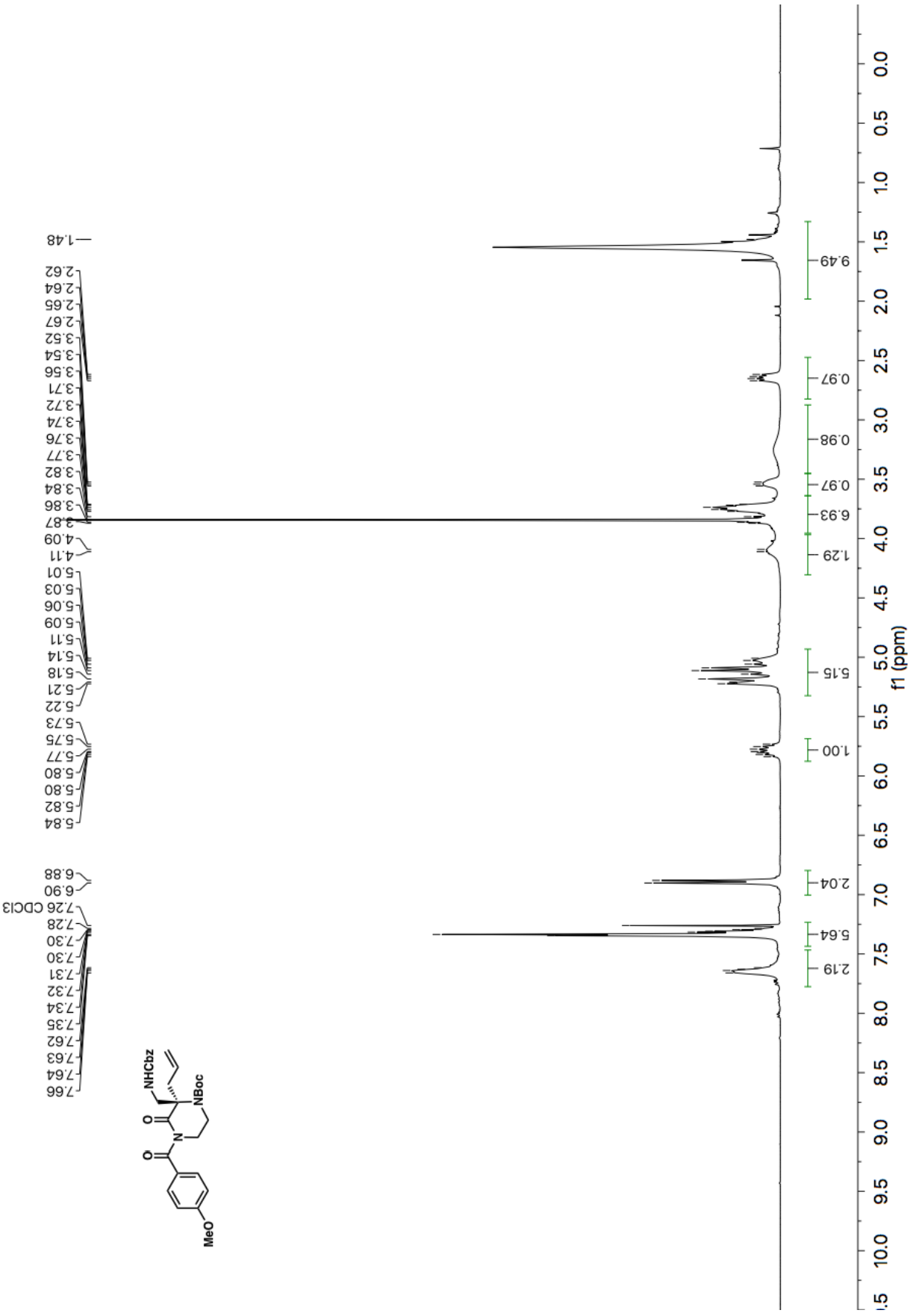
^{1}H NMR (400 MHz, $CDCl_3$) of compound **4k.**



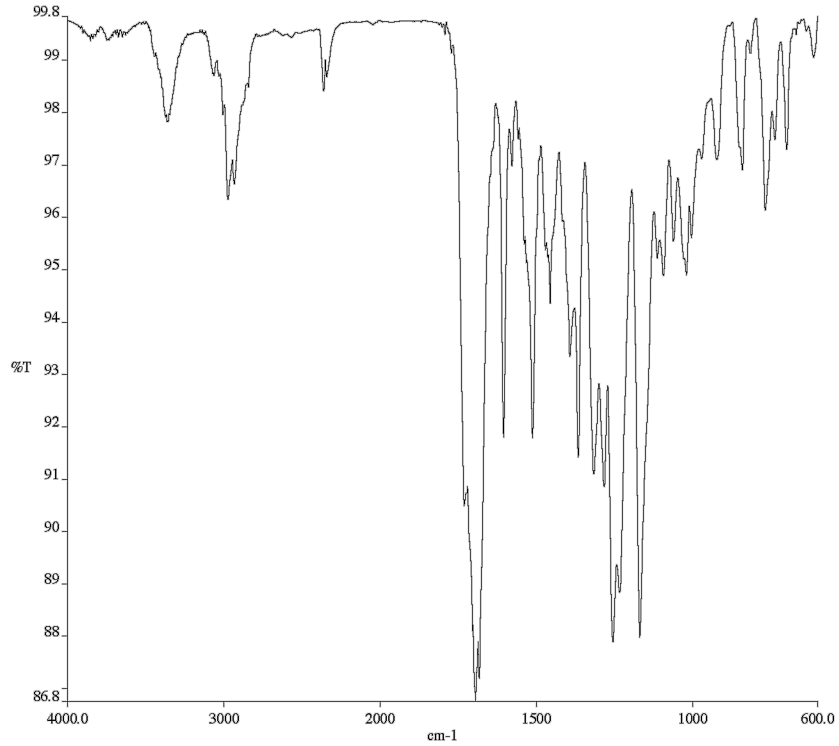
Infrared spectrum (Thin Film, NaCl) of compound **4k**.



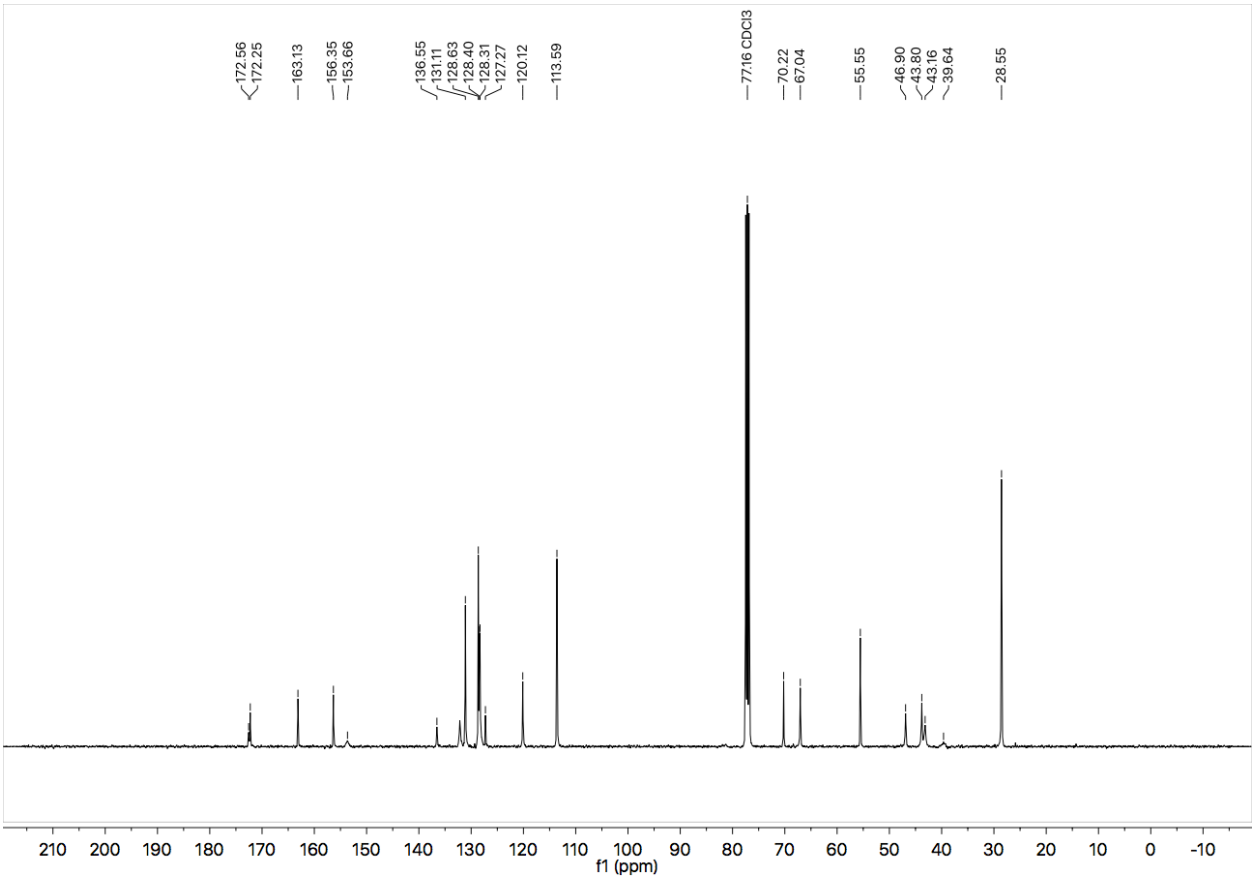
^{13}C NMR (101 MHz, $CDCl_3$) of compound **4k**.



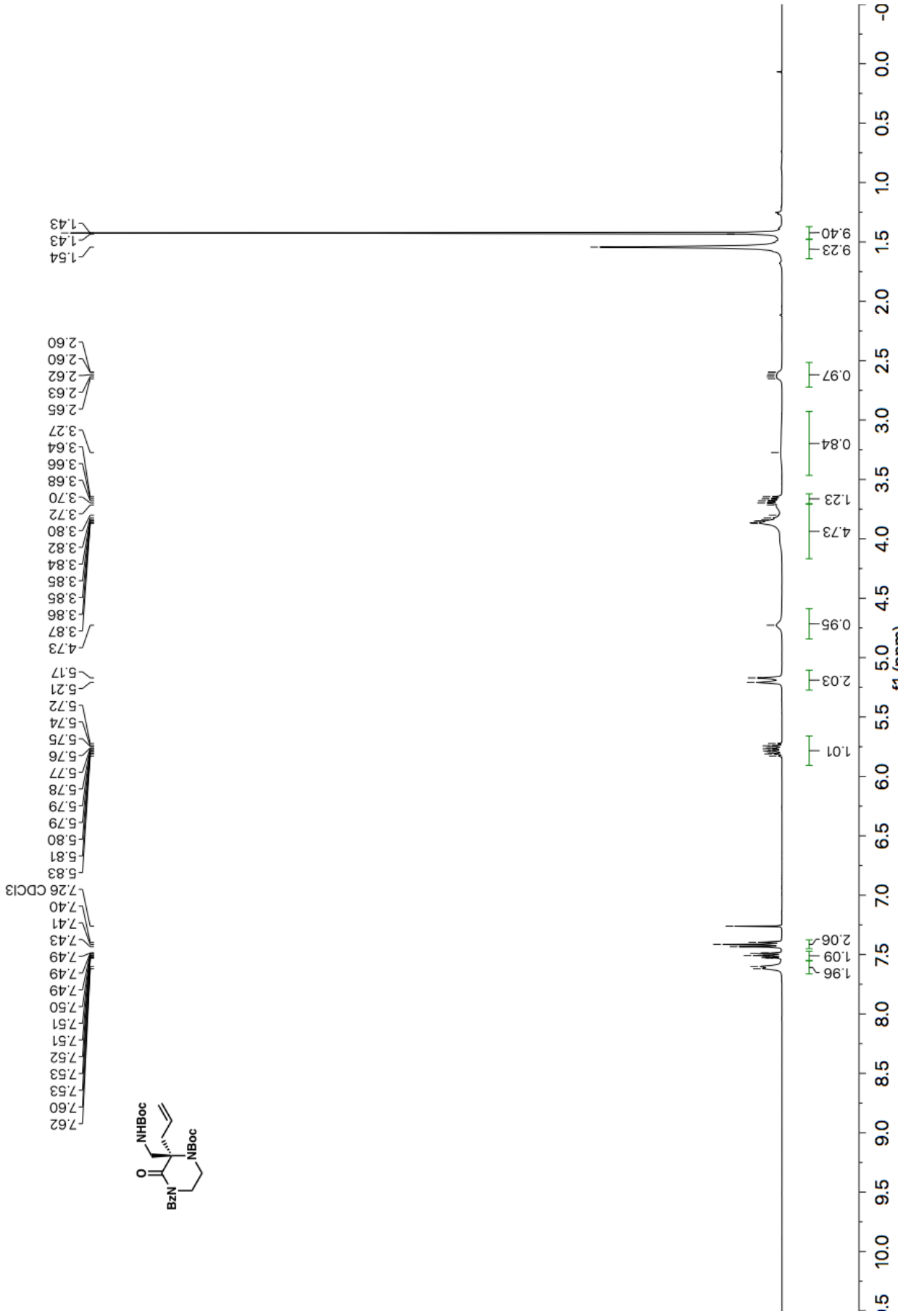
^{1}H NMR (400 MHz, $CDCl_3$) of compound **4l.**



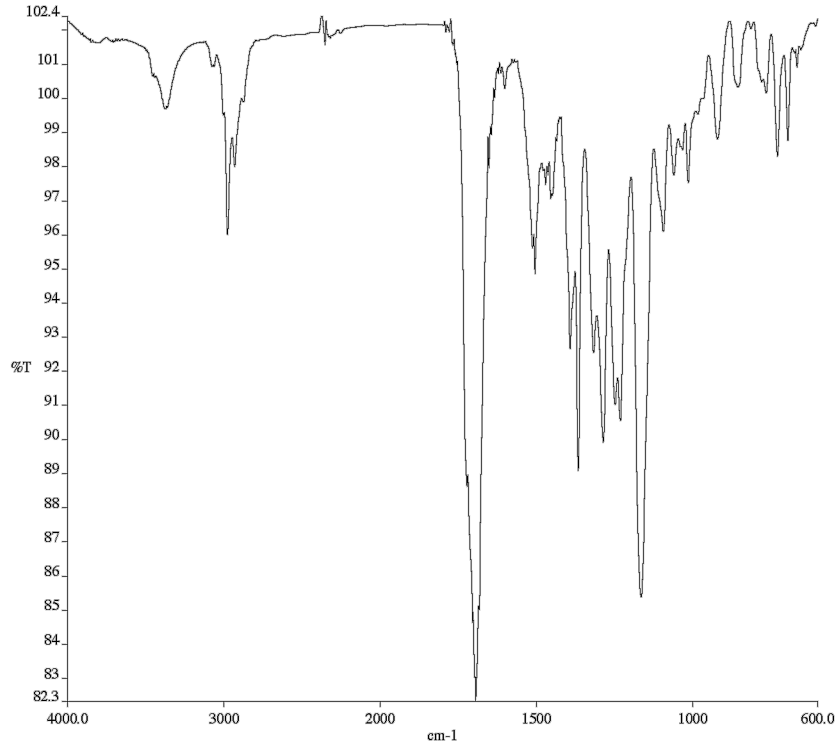
Infrared spectrum (Thin Film, NaCl) of compound **4l**.



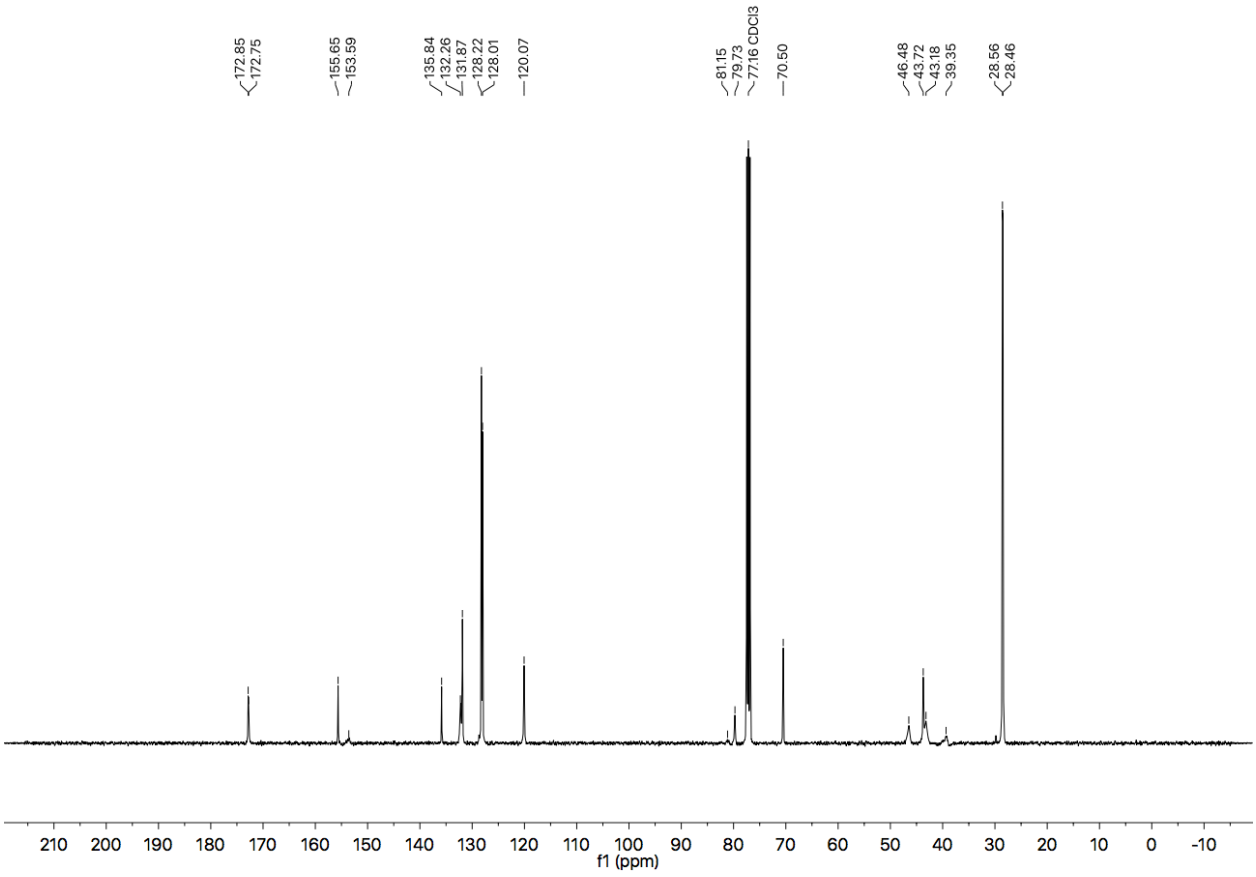
^{13}C NMR (101 MHz, $CDCl_3$) of compound **4l**.



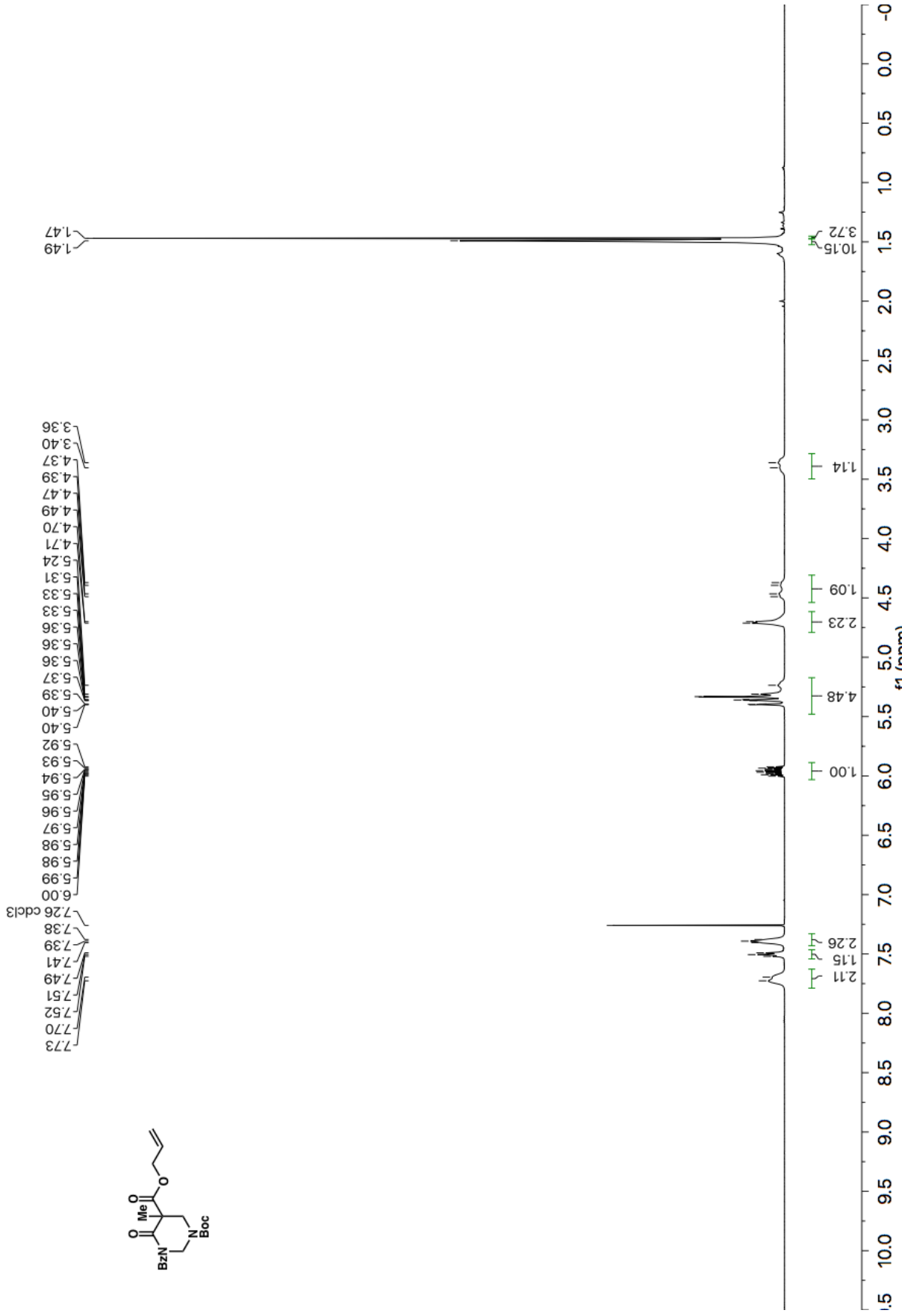
^{1}H NMR (400 MHz, $CDCl_3$) of compound **4m.**



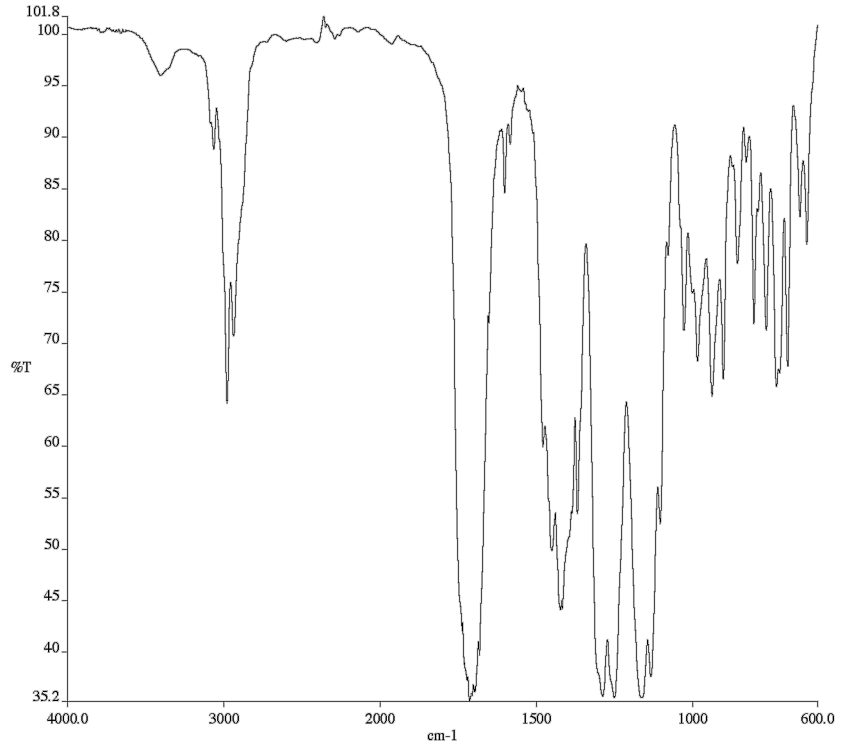
Infrared spectrum (Thin Film, NaCl) of compound **4m**.



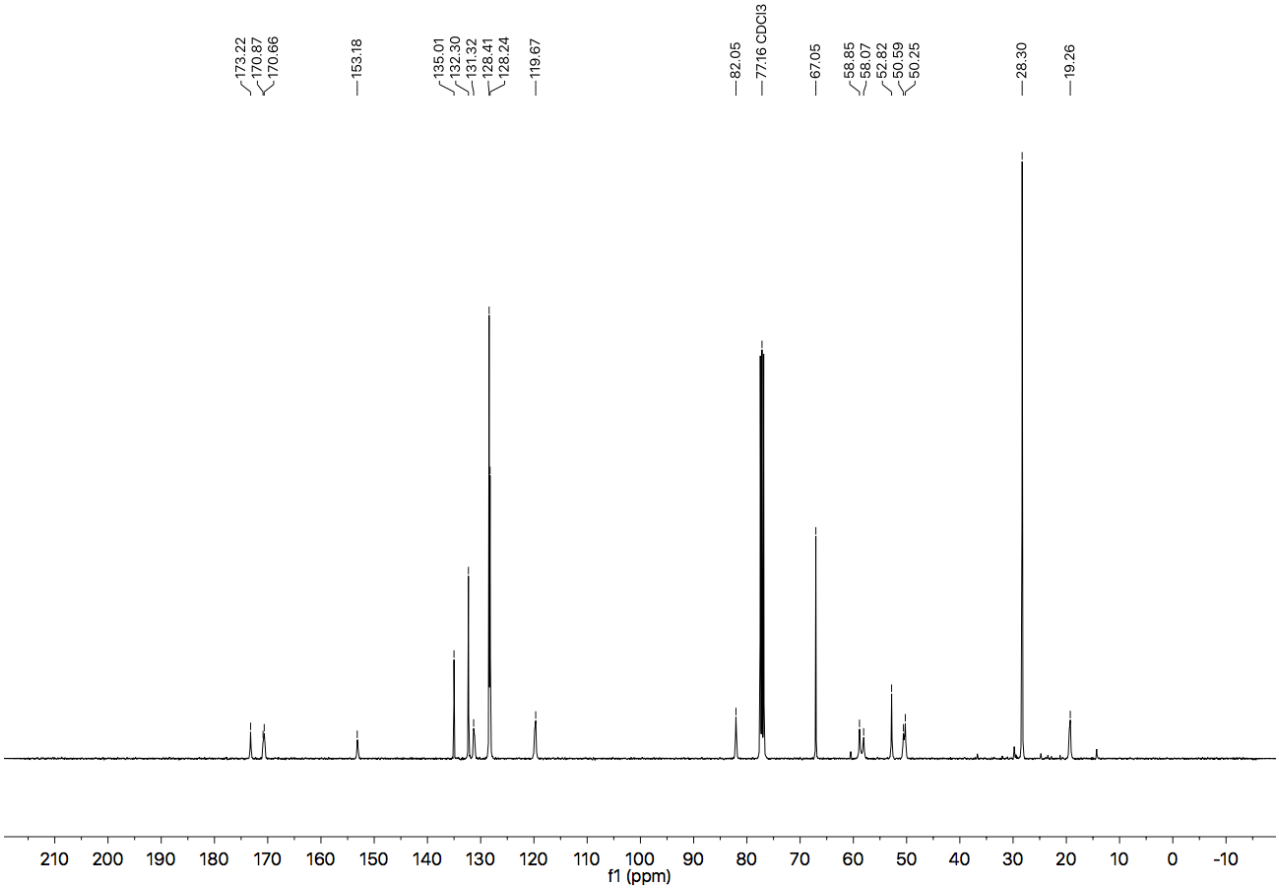
^{13}C NMR (101 MHz, $CDCl_3$) of compound **4m**.



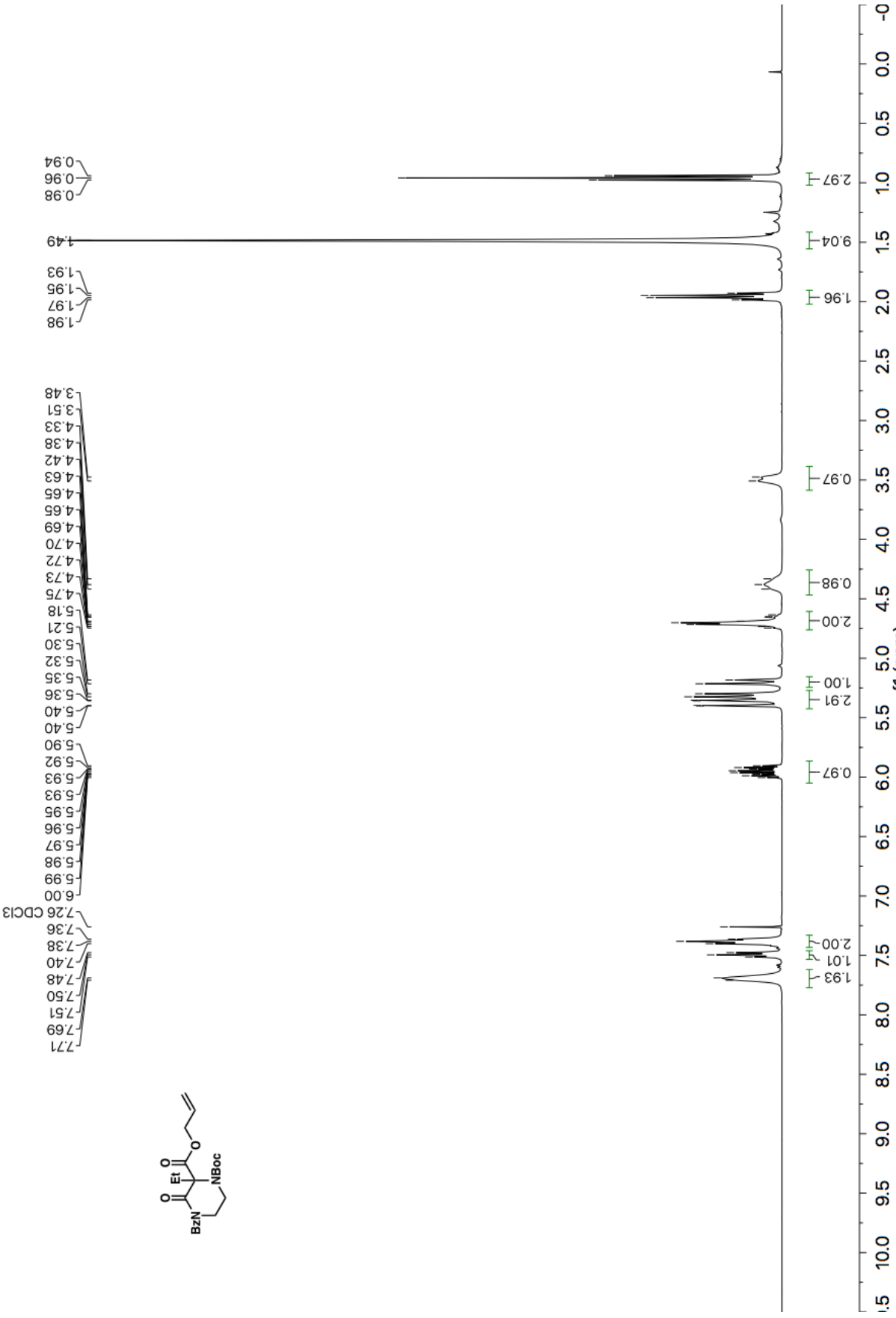
^{1}H NMR (500 MHz, $CDCl_3$) of compound **5a.**



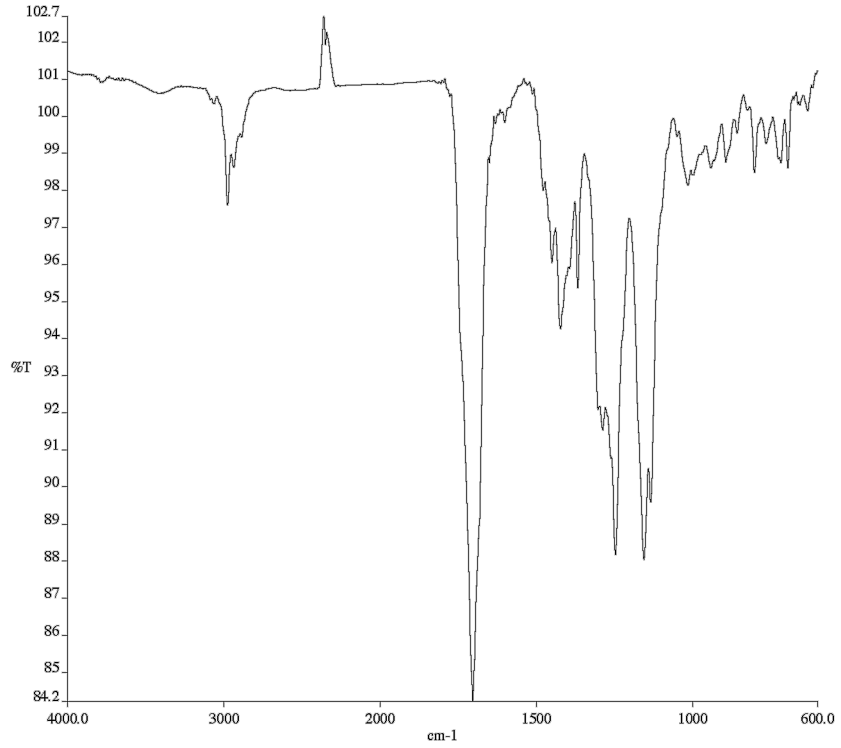
Infrared spectrum (Thin Film, NaCl) of compound **5a**.



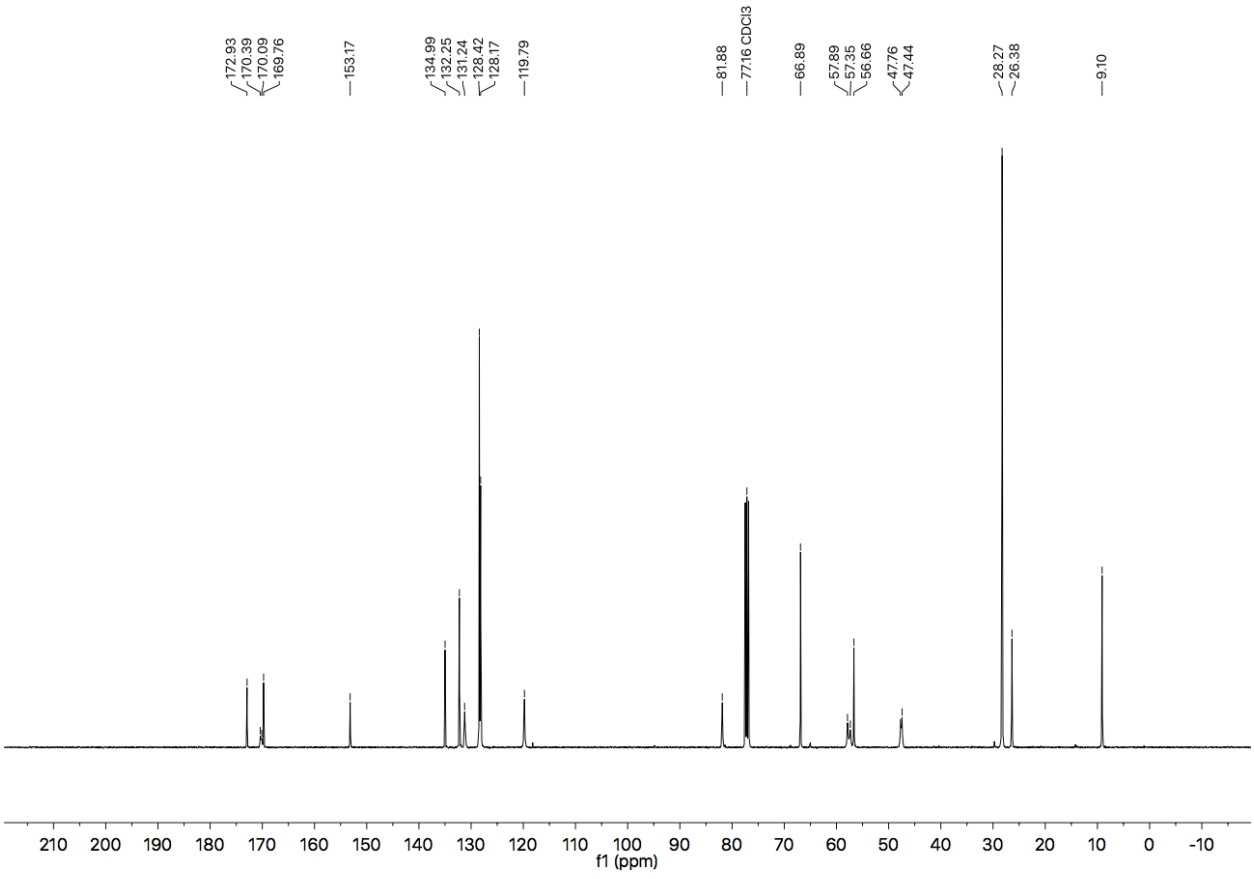
^{13}C NMR (101 MHz, $CDCl_3$) of compound **5a**.



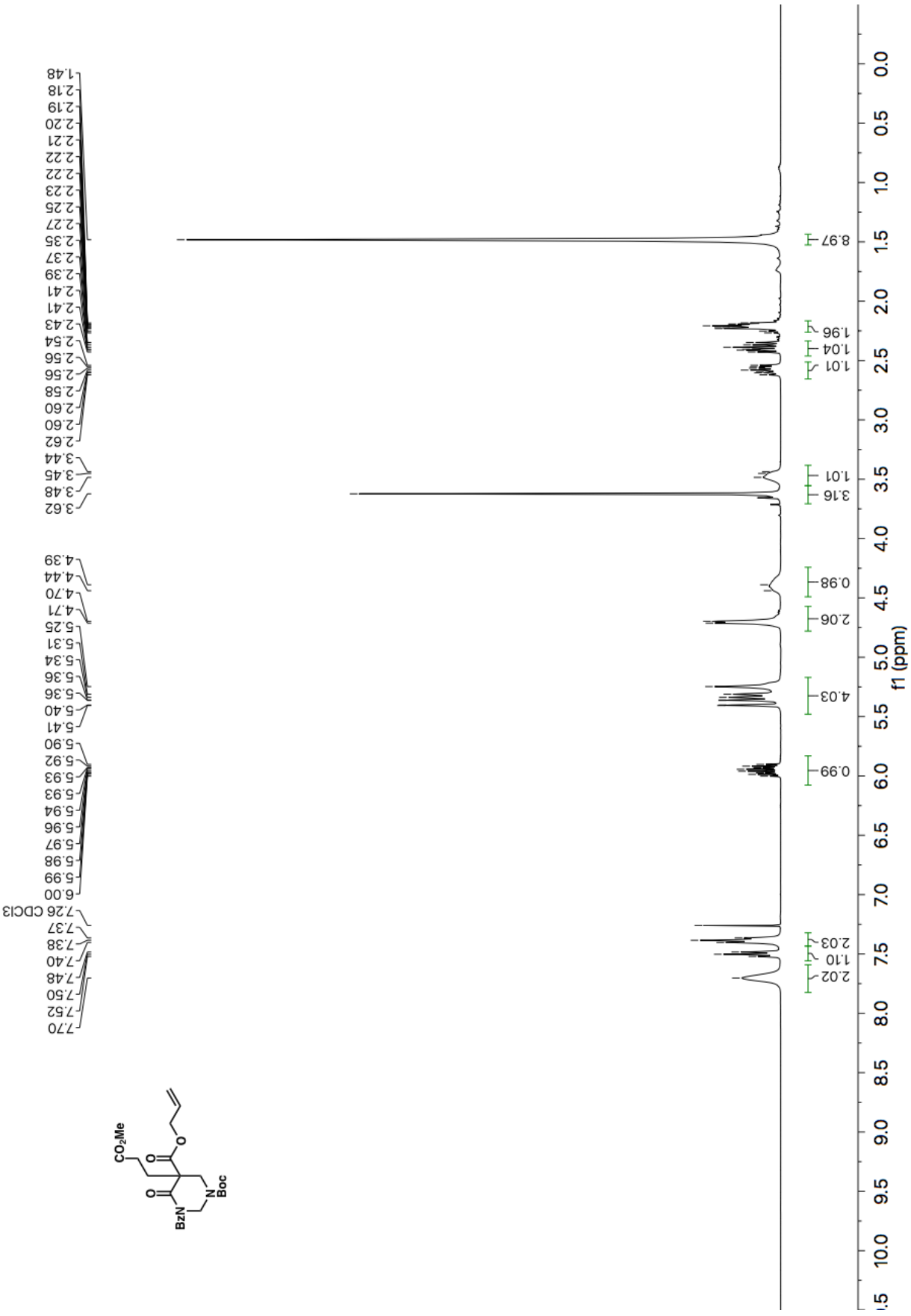
^{1}H NMR (400 MHz, $CDCl_3$) of compound **5b.**



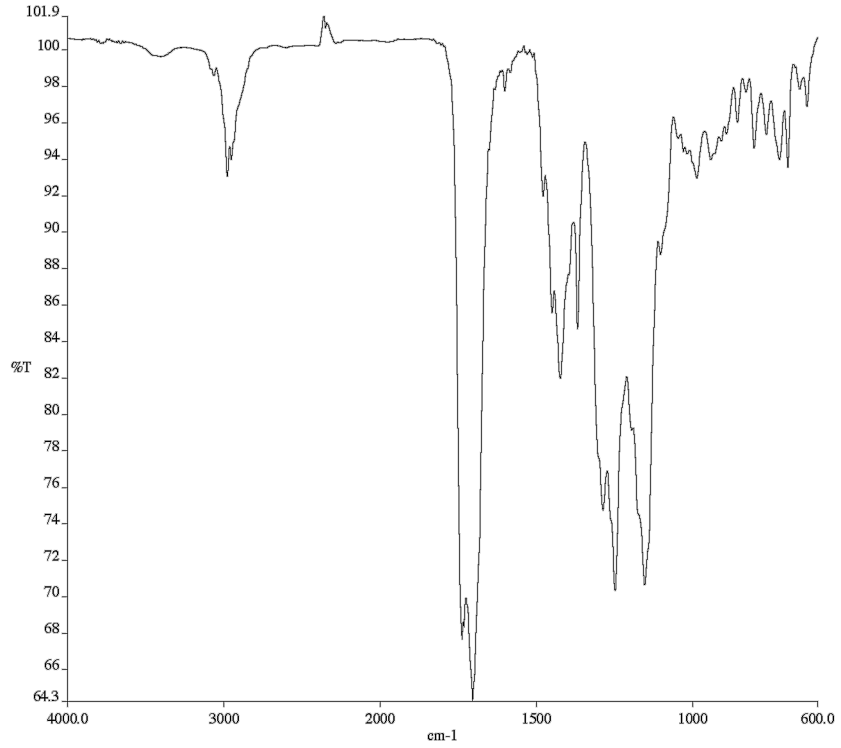
Infrared spectrum (Thin Film, NaCl) of compound **5b**.



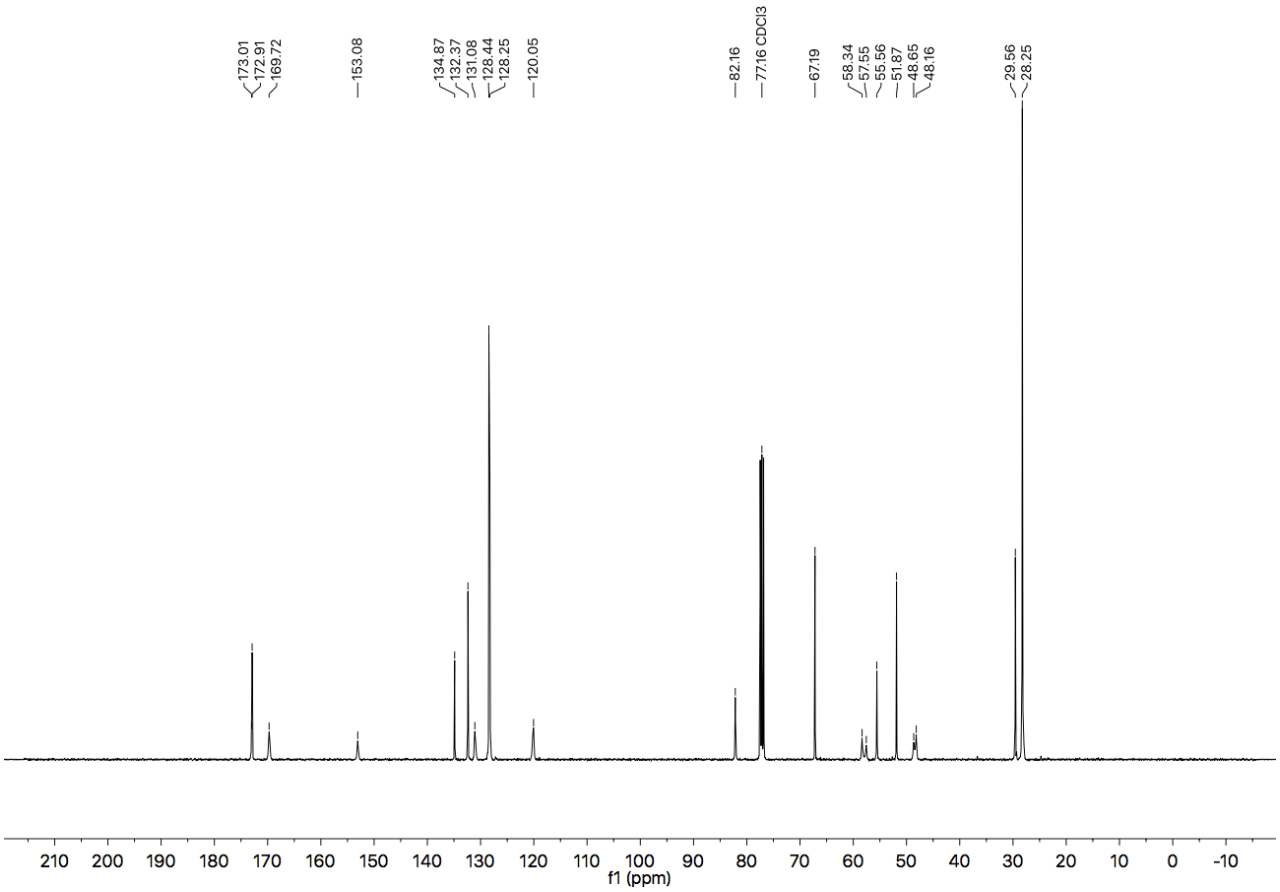
^{13}C NMR (101 MHz, $CDCl_3$) of compound **5b**.



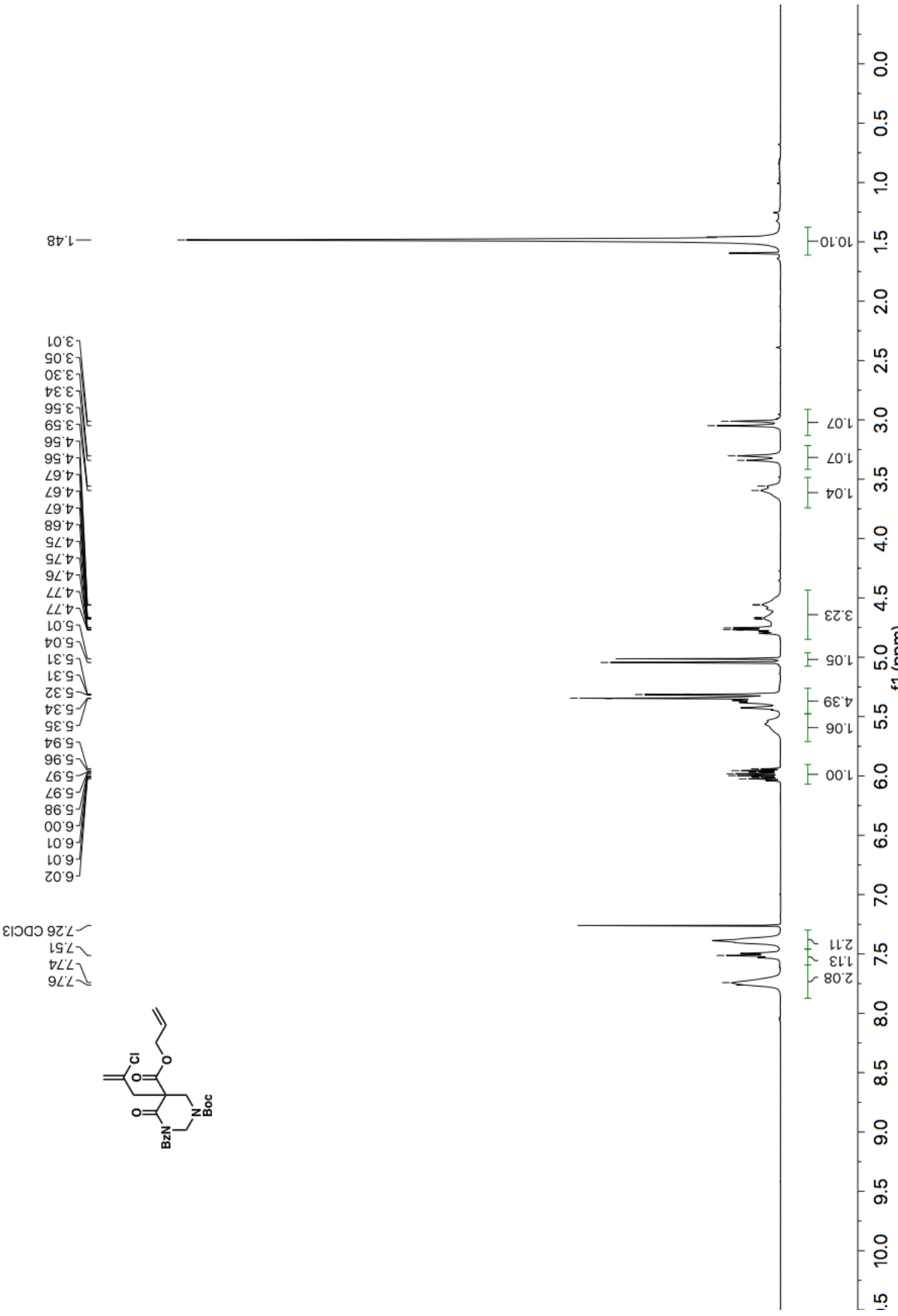
^{1}H NMR (400 MHz, $CDCl_3$) of compound **5c.**



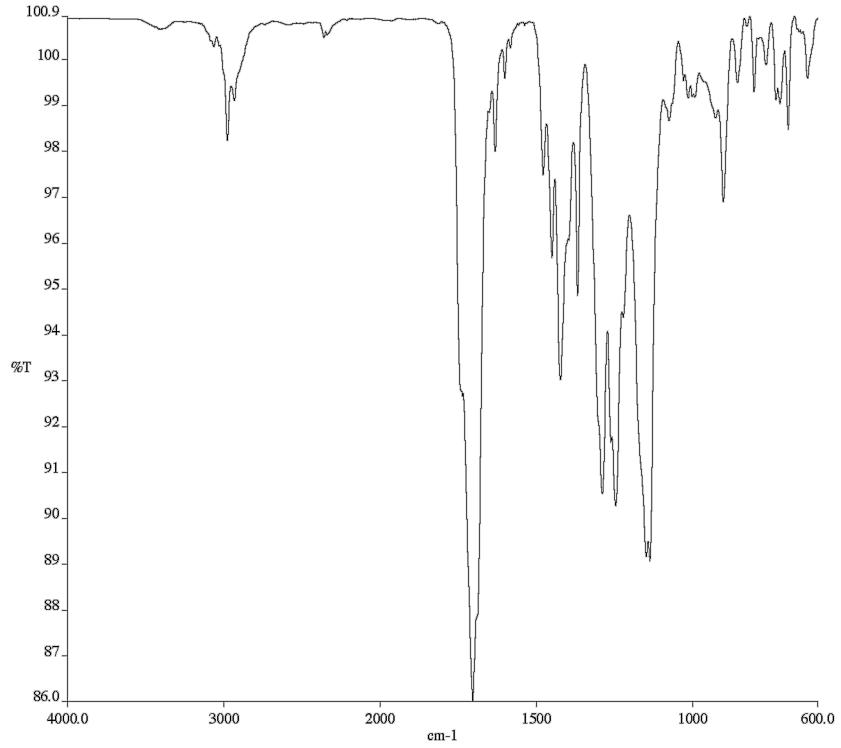
Infrared spectrum (Thin Film, NaCl) of compound **5c**.



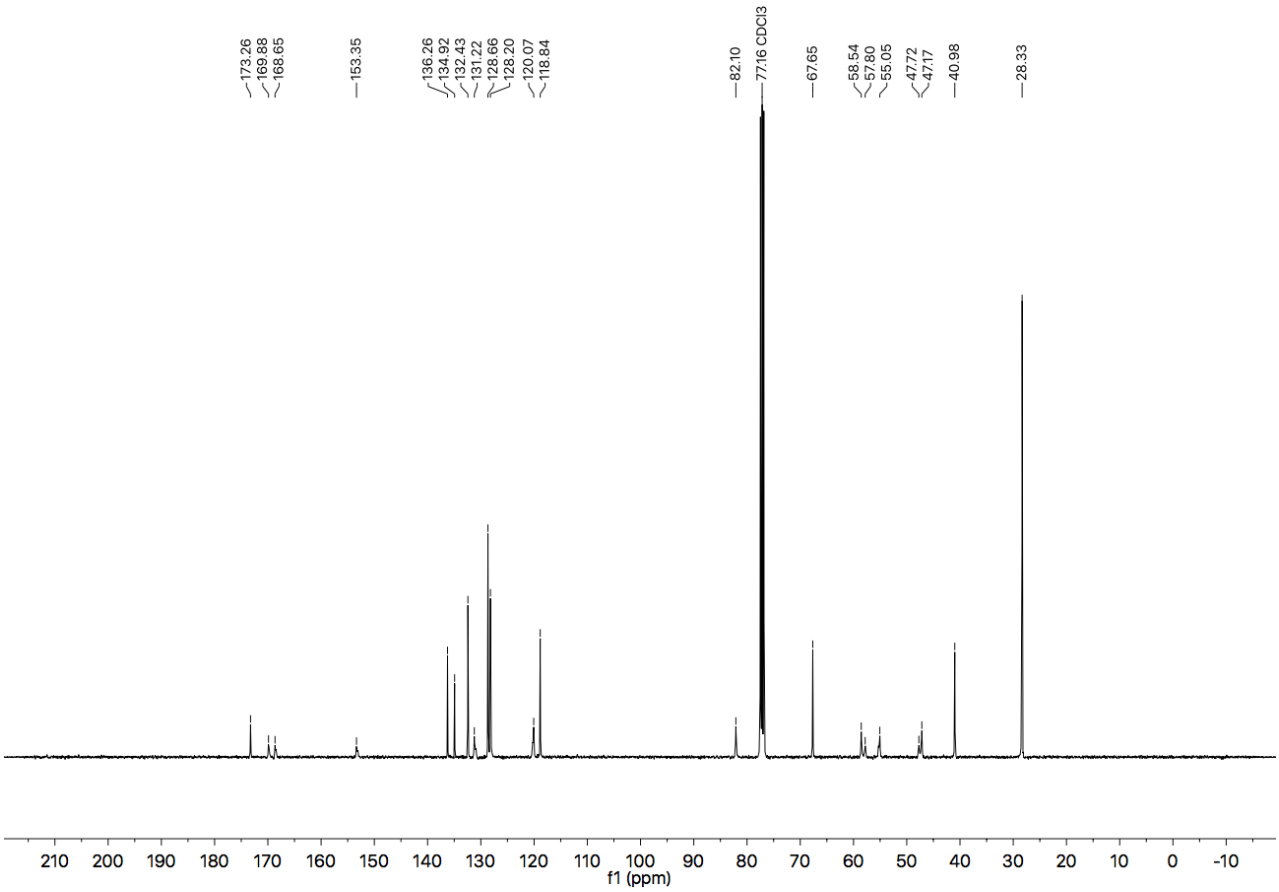
^{13}C NMR (101 MHz, $CDCl_3$) of compound **5c**.



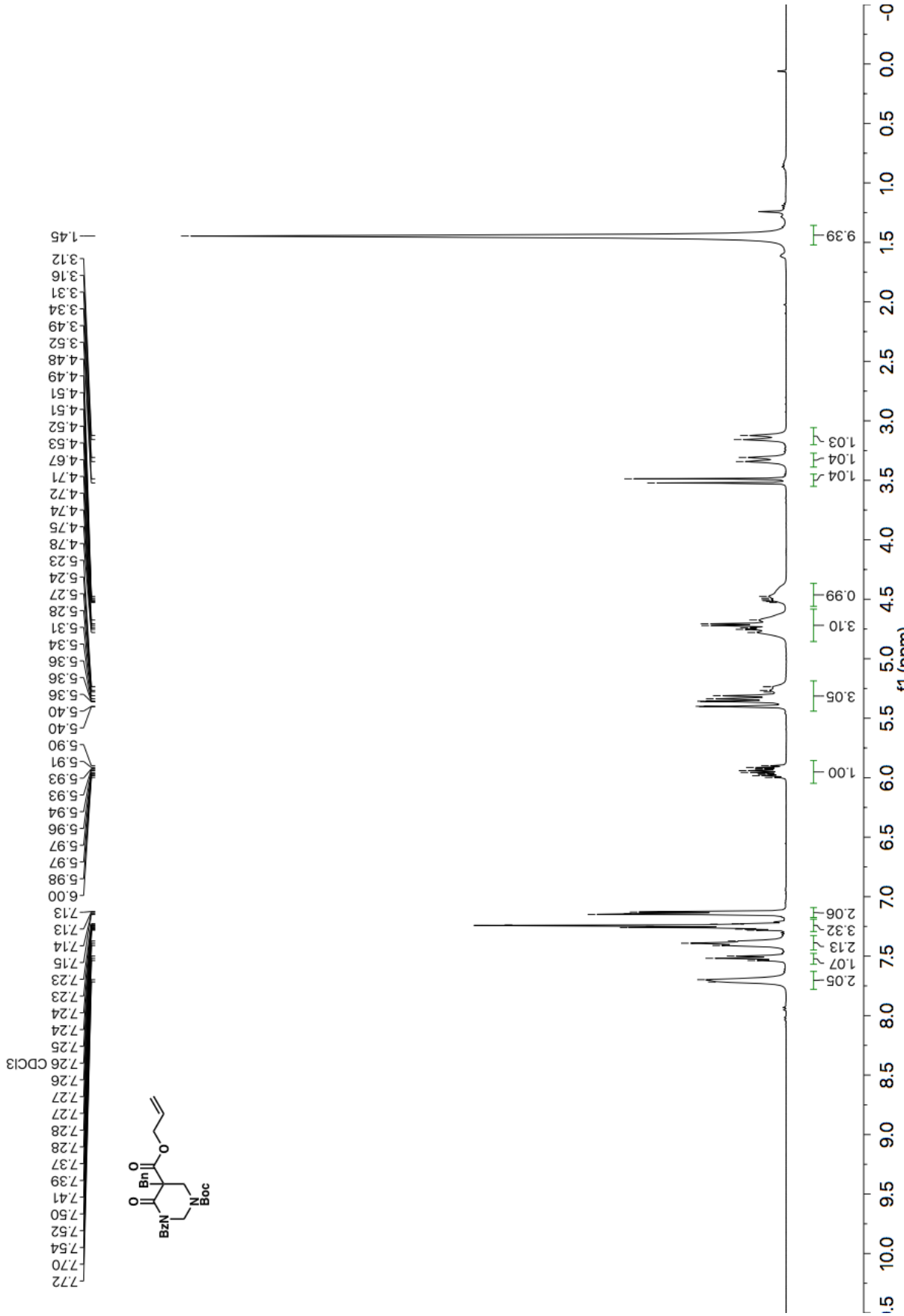
^{1}H NMR (400 MHz, $CDCl_3$) of compound **5d.**



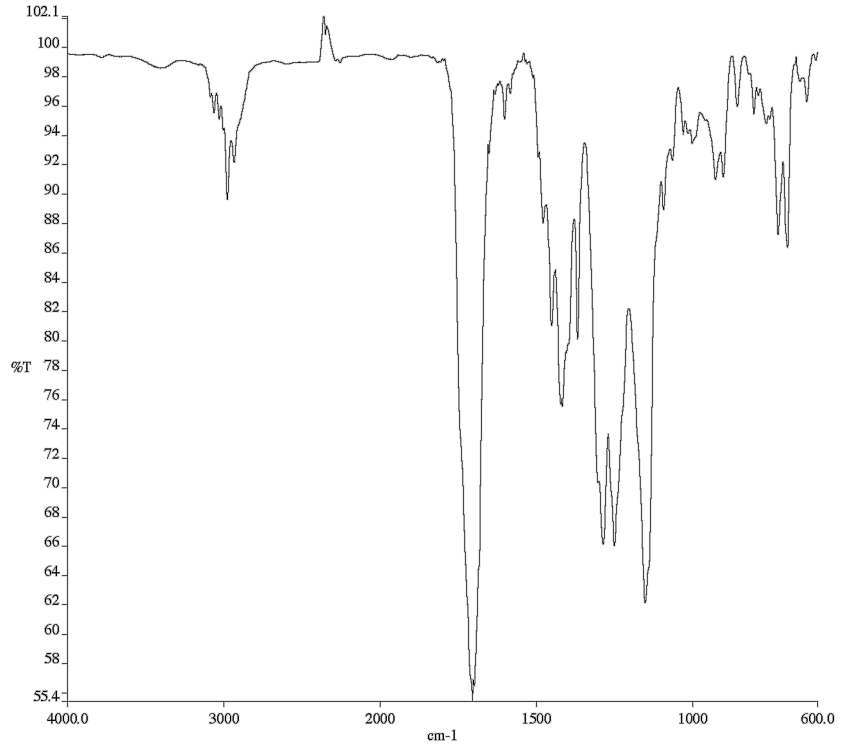
Infrared spectrum (Thin Film, NaCl) of compound **5d**.



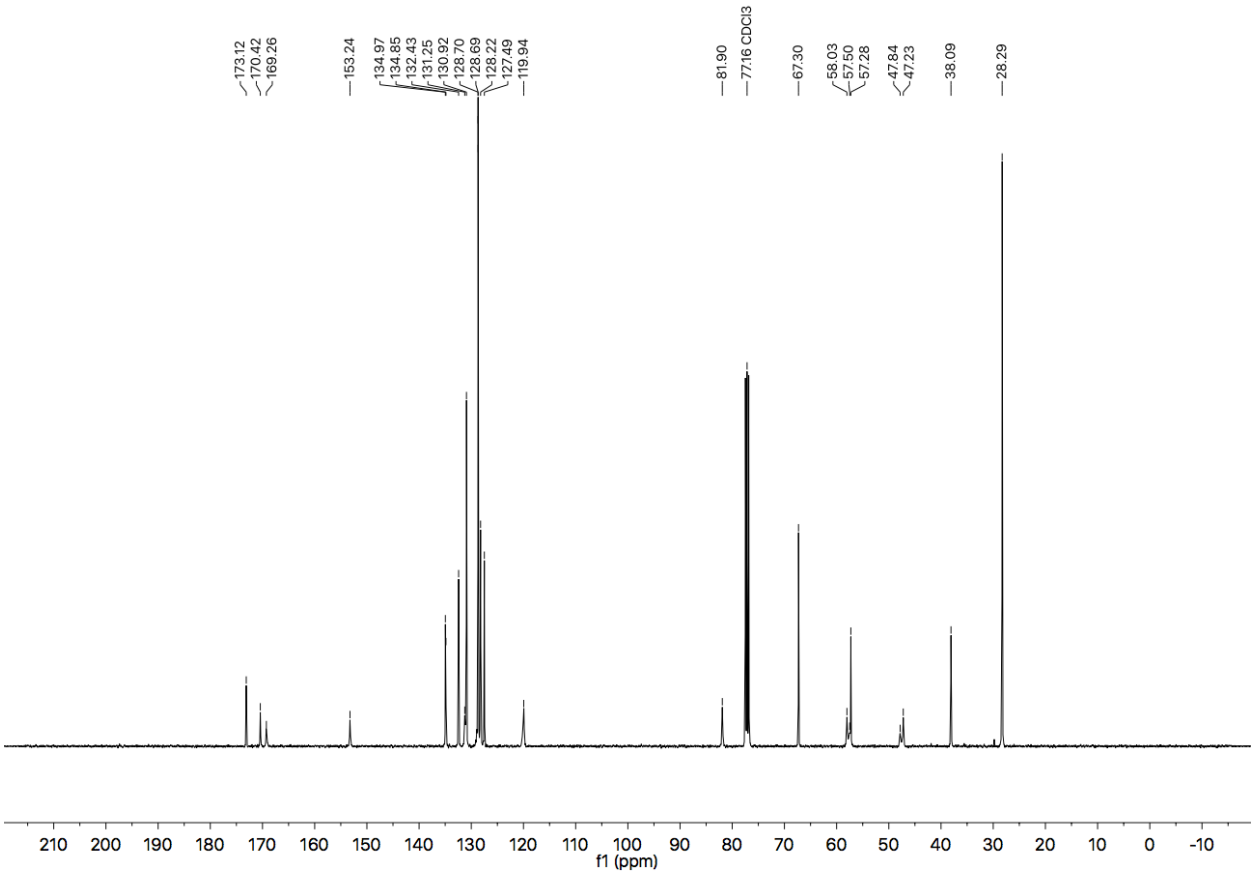
^{13}C NMR (101 MHz, $CDCl_3$) of compound **5d**.



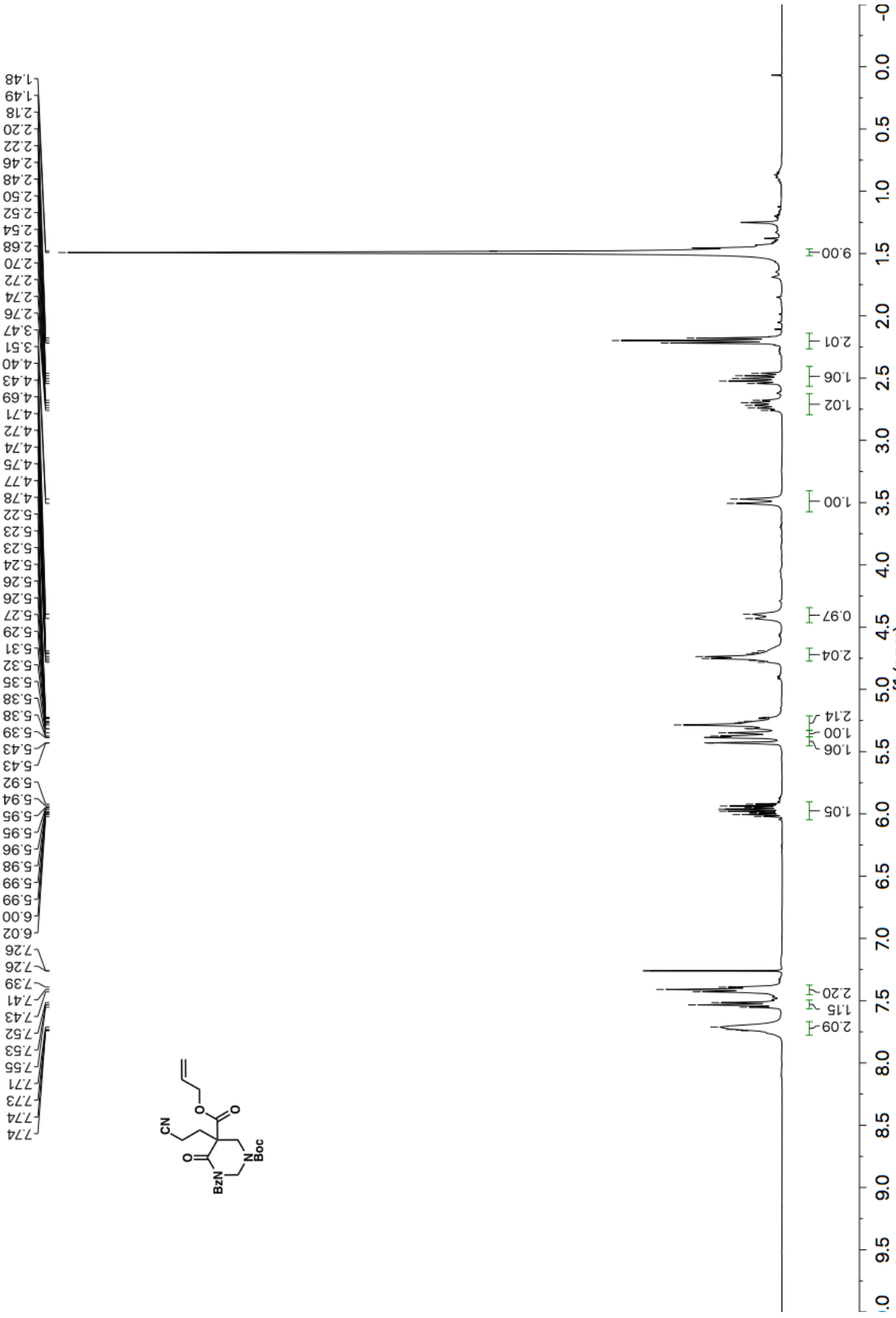
^{1}H NMR (400 MHz, $CDCl_3$) of compound **5e.**



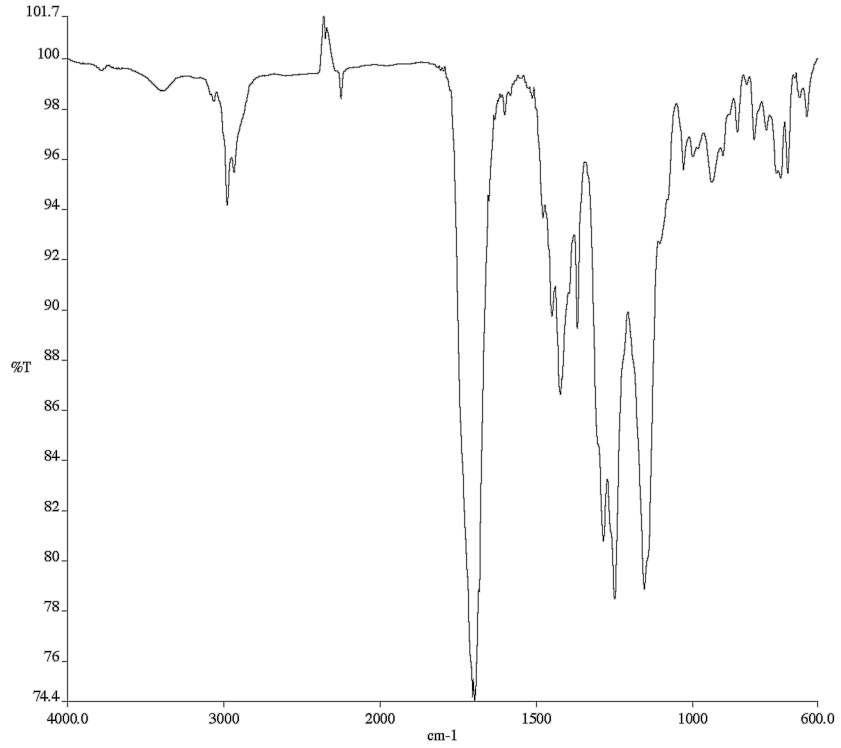
Infrared spectrum (Thin Film, NaCl) of compound **5e**.



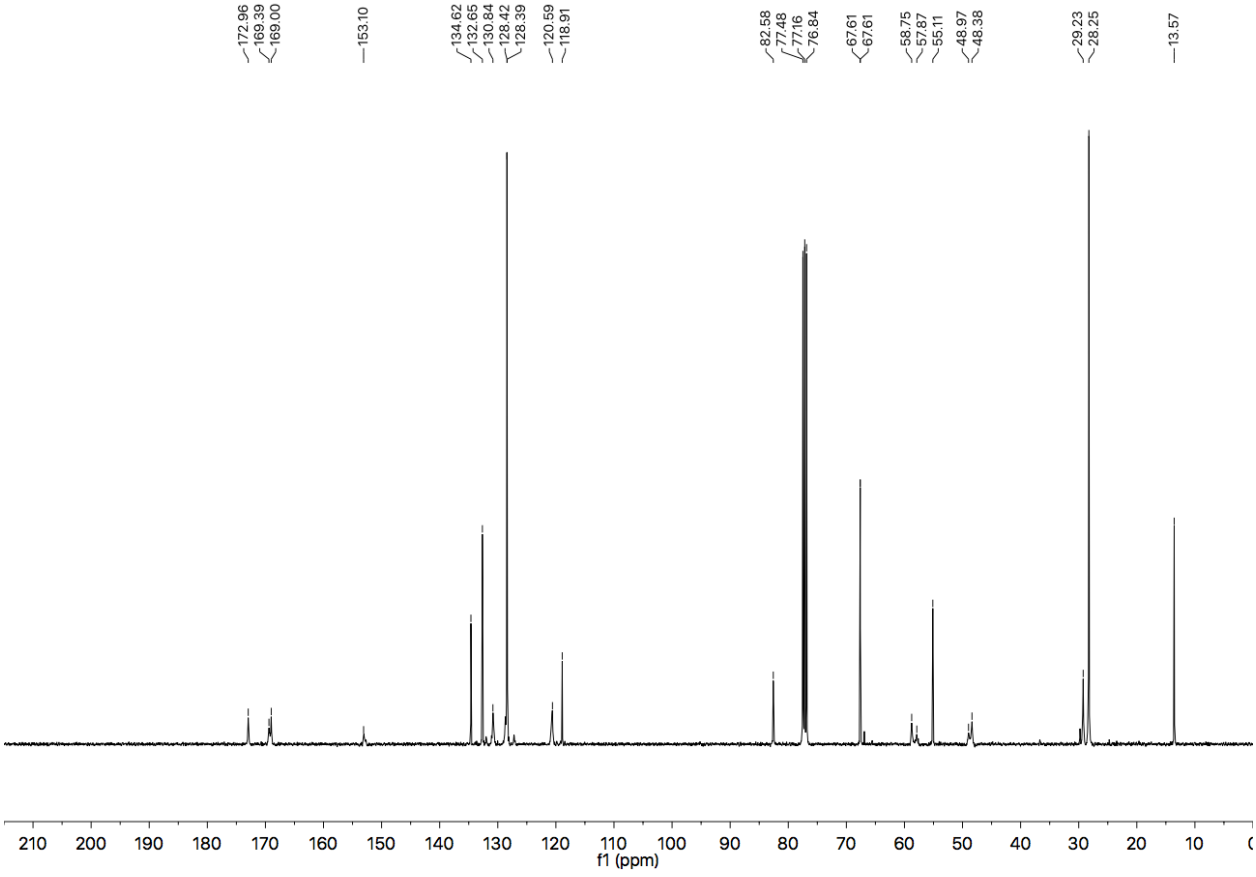
^{13}C NMR (101 MHz, $CDCl_3$) of compound **5e**.



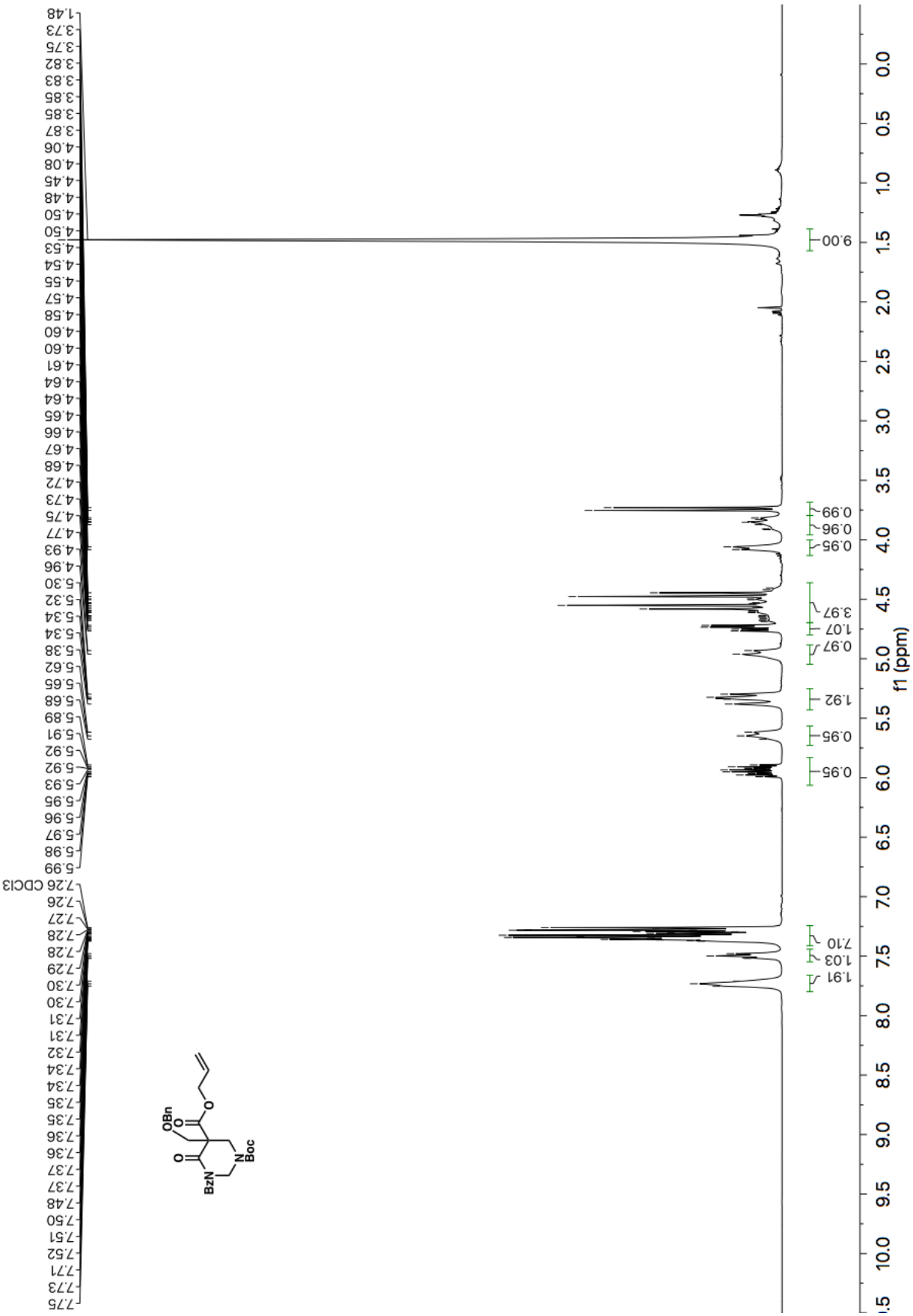
^{1}H NMR (400 MHz, $CDCl_3$) of compound **5f.**



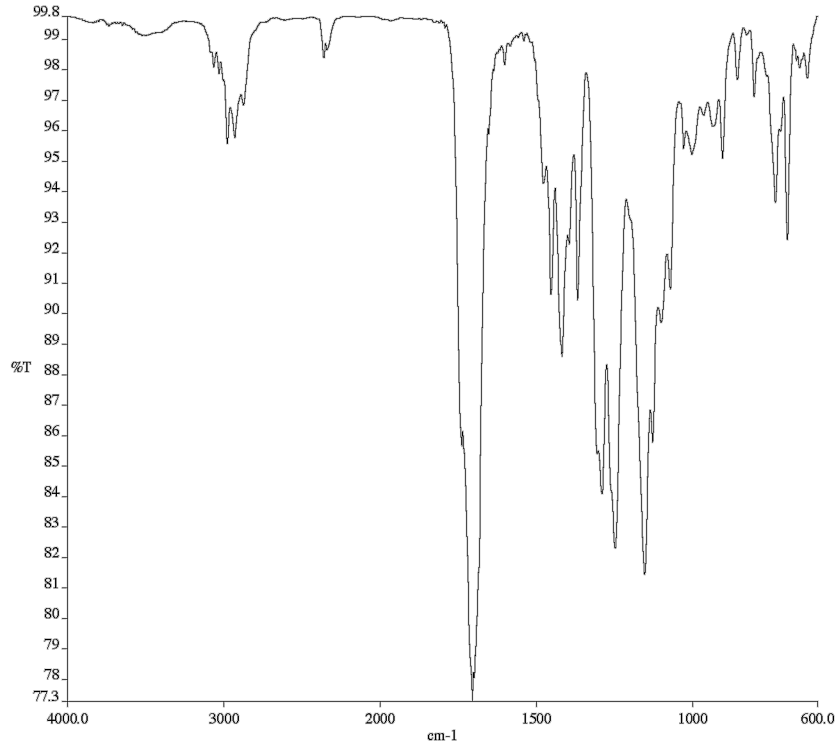
Infrared spectrum (Thin Film, NaCl) of compound **5f**.



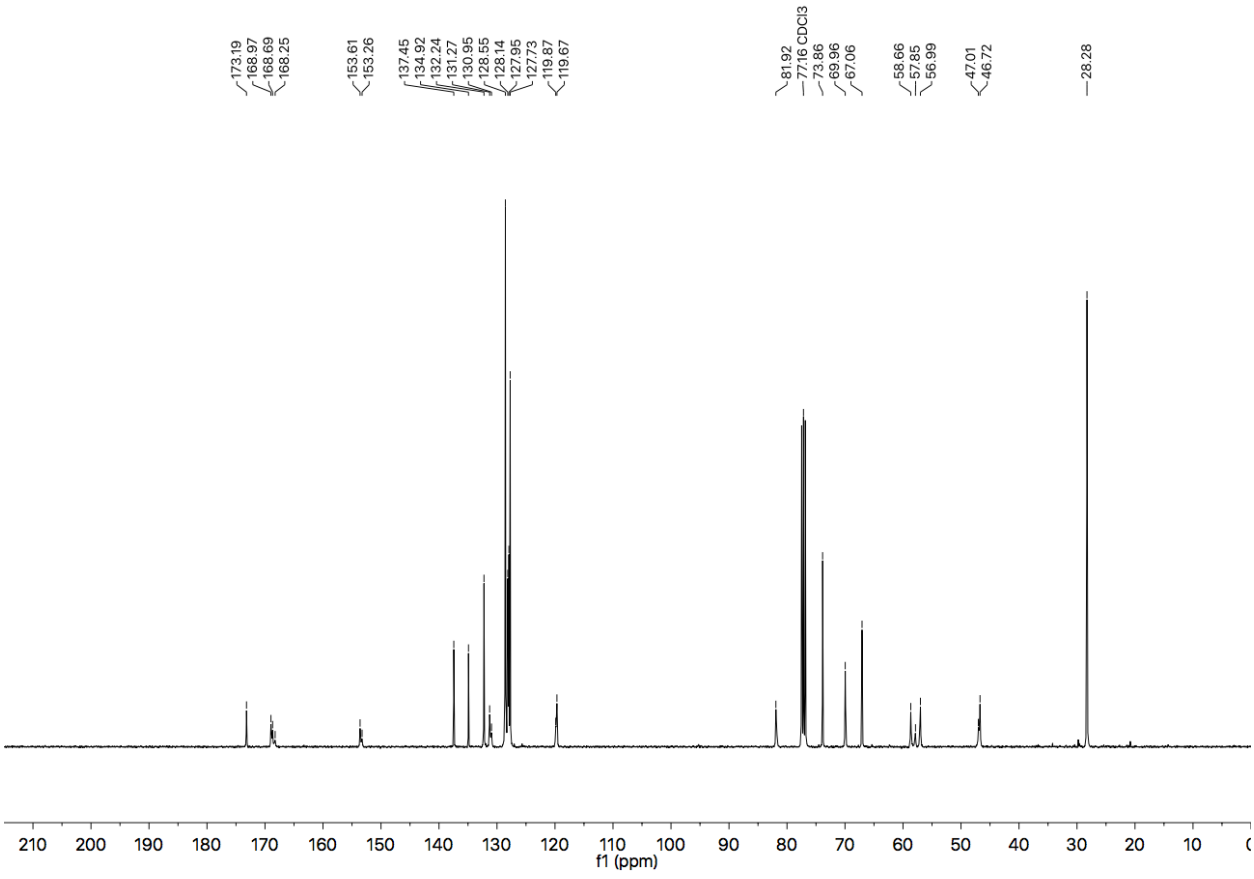
^{13}C NMR (101 MHz, $CDCl_3$) of compound **5f**.



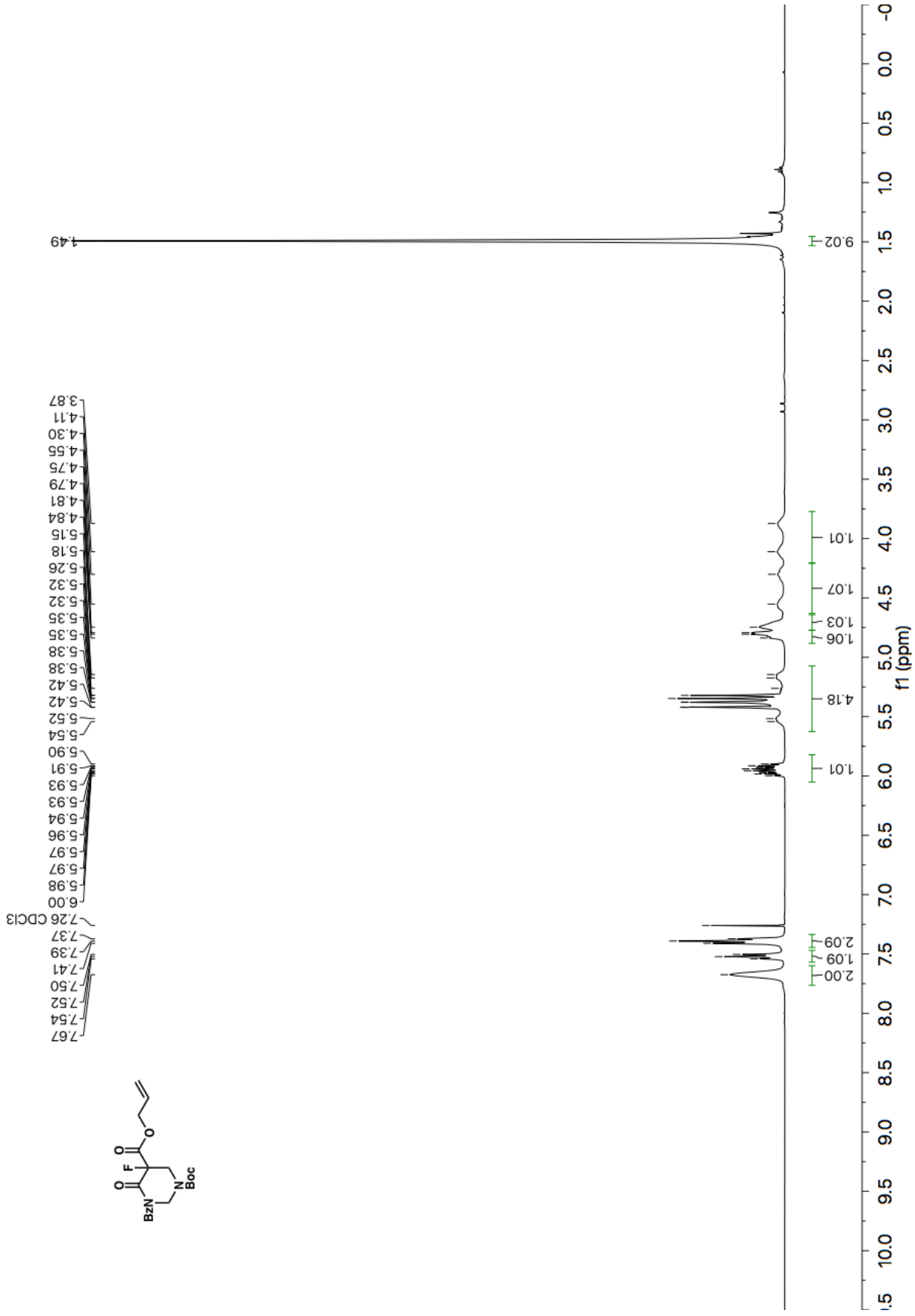
^{1}H NMR (400 MHz, $CDCl_3$) of compound **5g.**



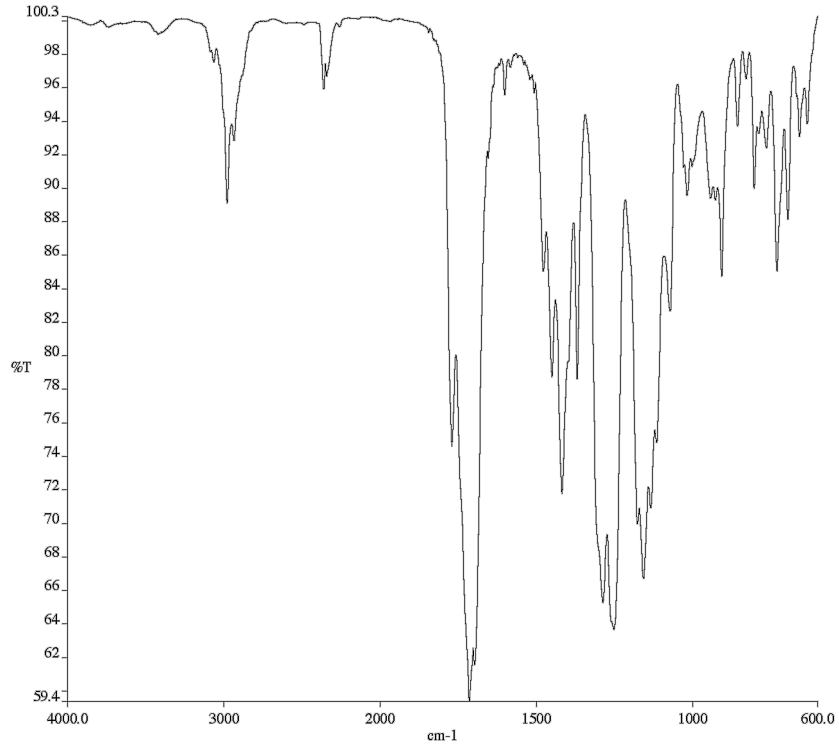
Infrared spectrum (Thin Film, NaCl) of compound **5g**.



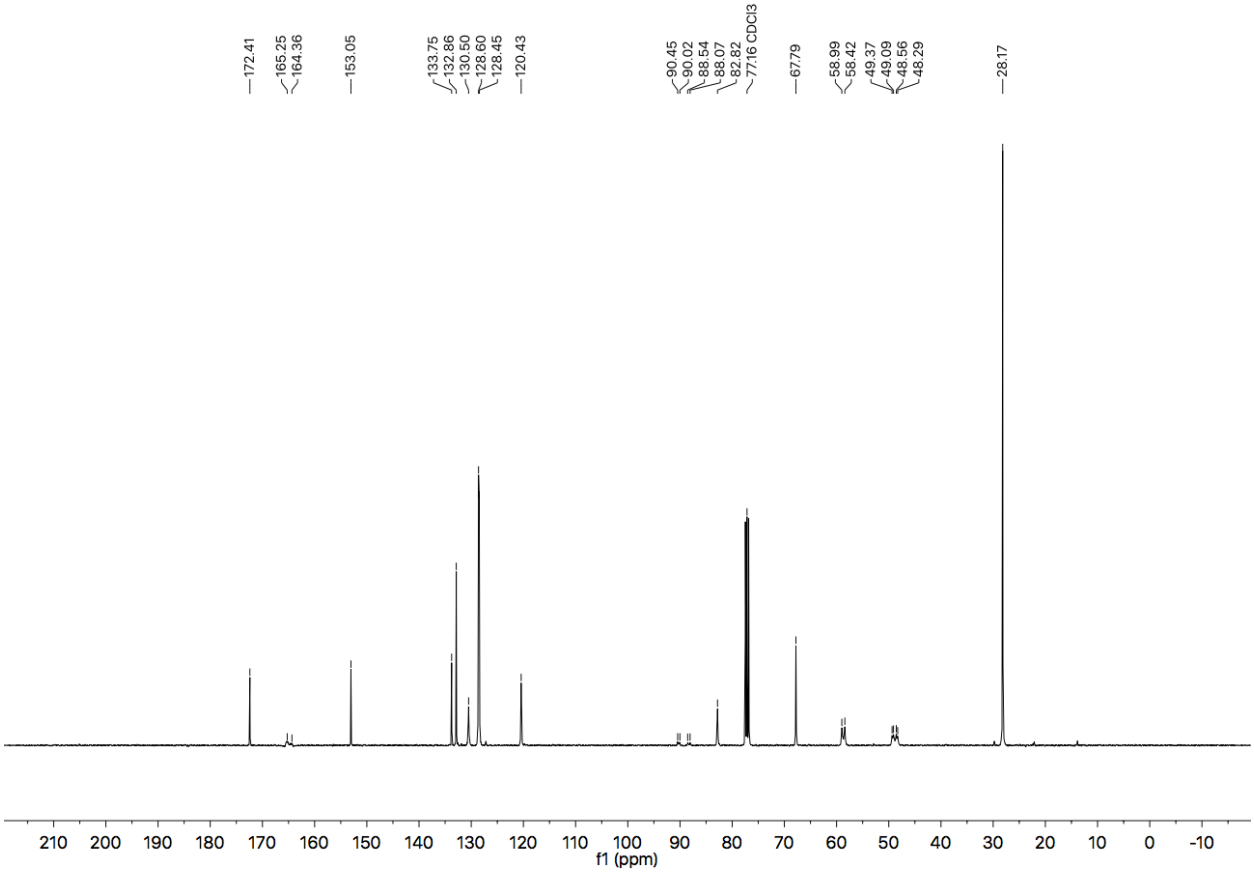
^{13}C NMR (101 MHz, $CDCl_3$) of compound **5g**.



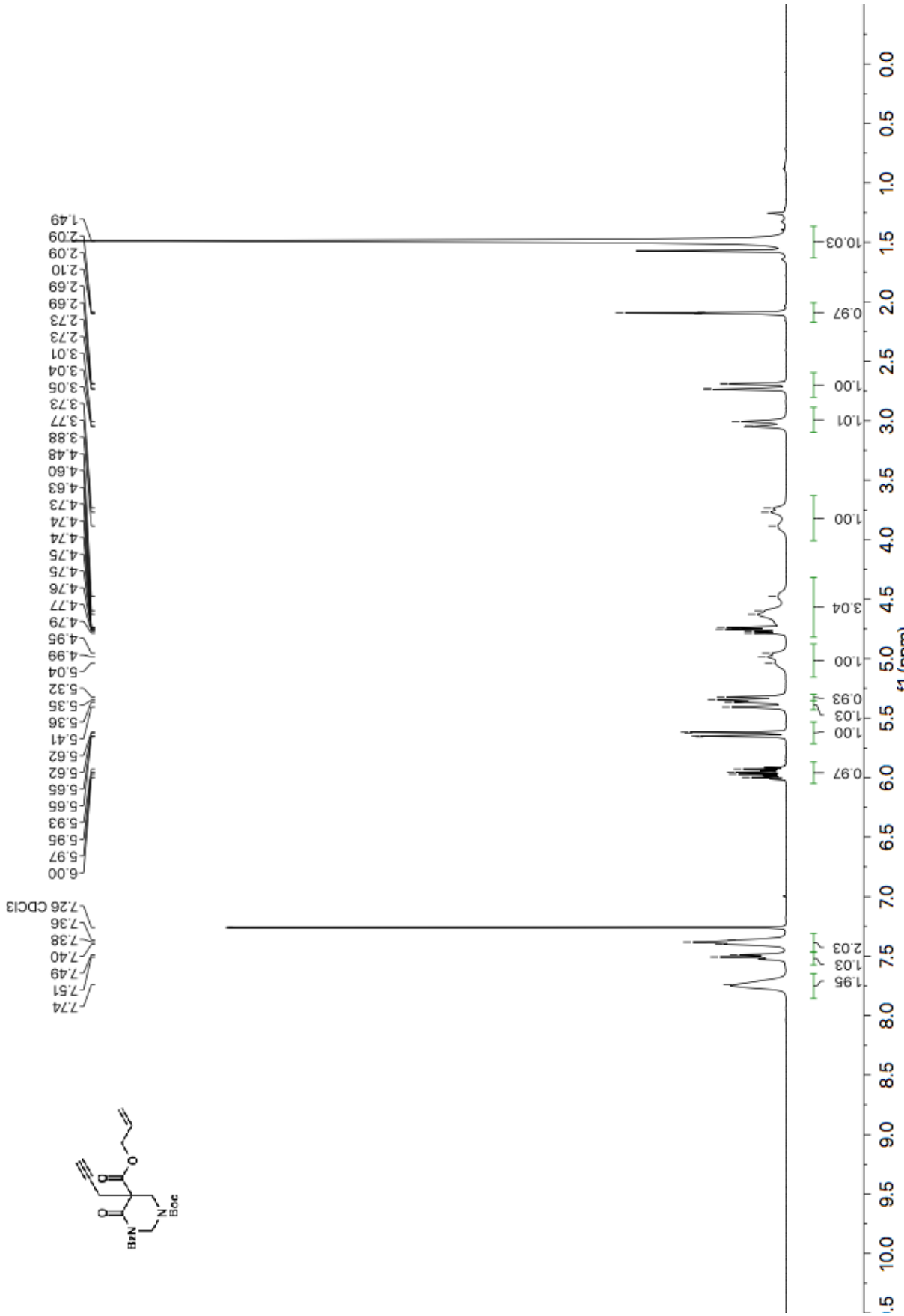
^{1}H NMR (400 MHz, $CDCl_3$) of compound **5h.**



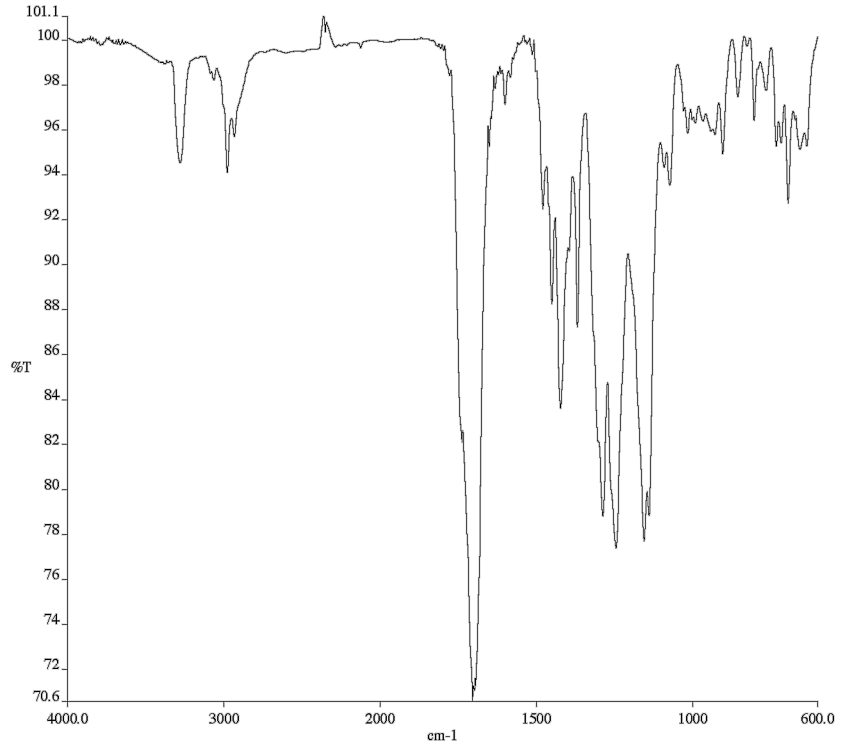
Infrared spectrum (Thin Film, NaCl) of compound **5h**.



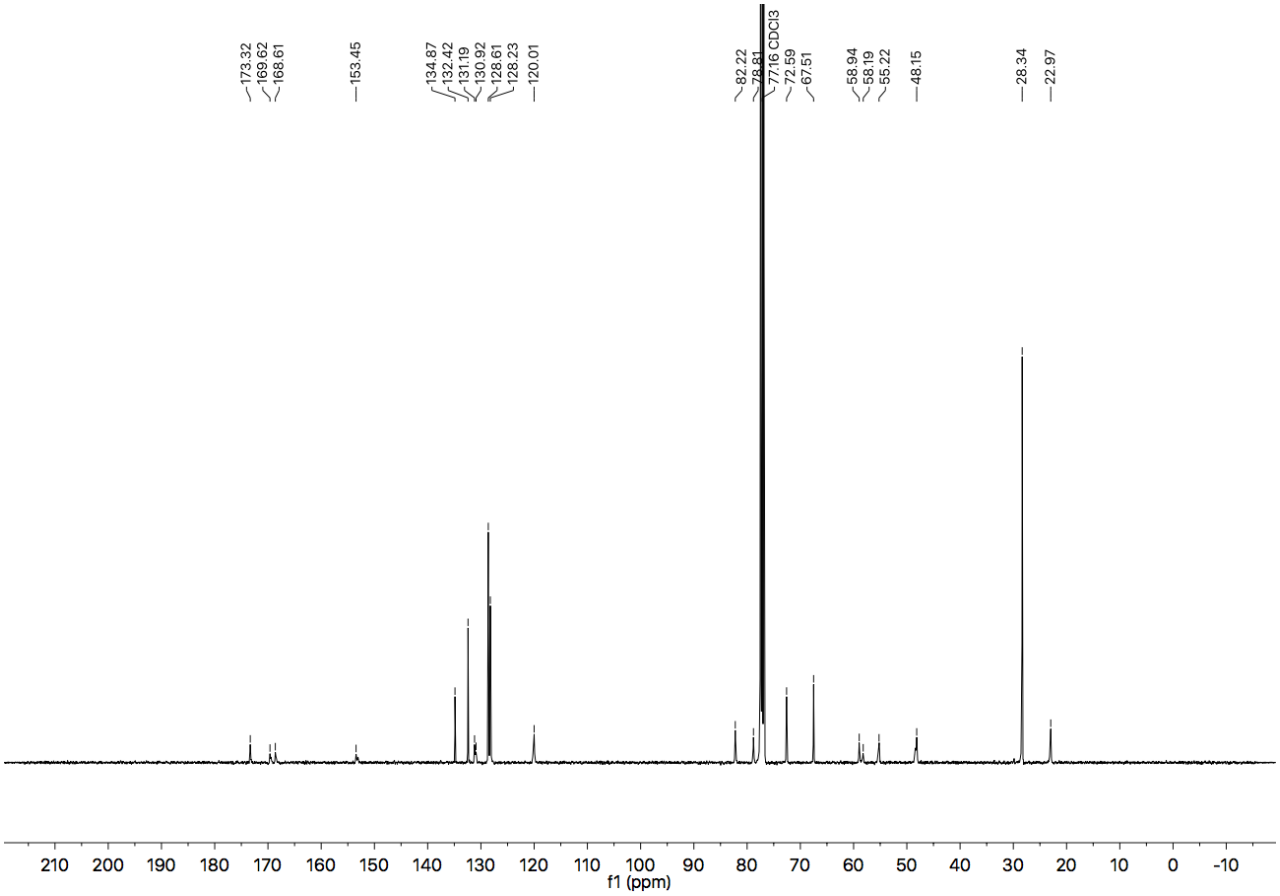
^{13}C NMR (101 MHz, $CDCl_3$) of compound **5h**.



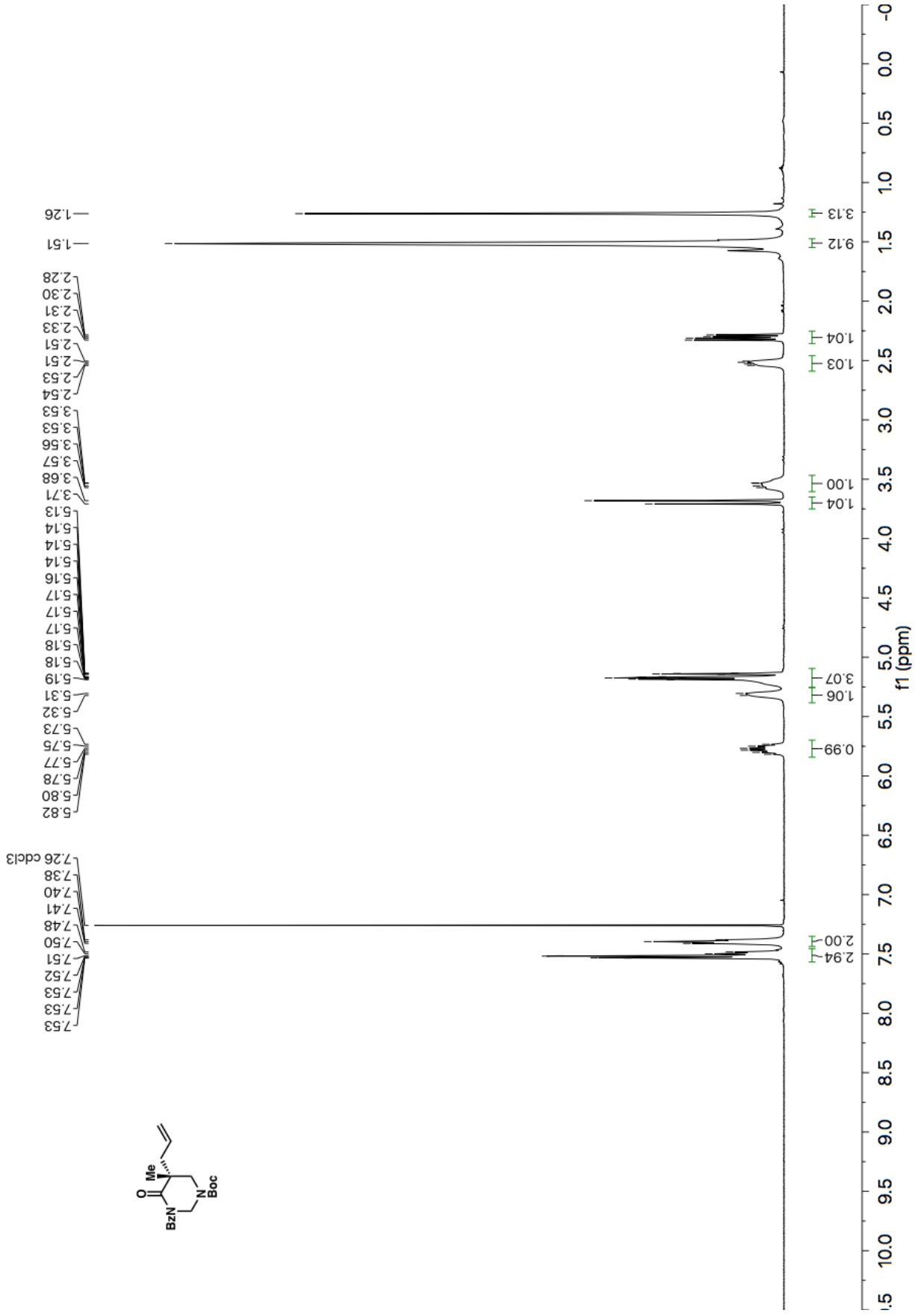
^{1}H NMR (400 MHz, $CDCl_3$) of compound **5i.**



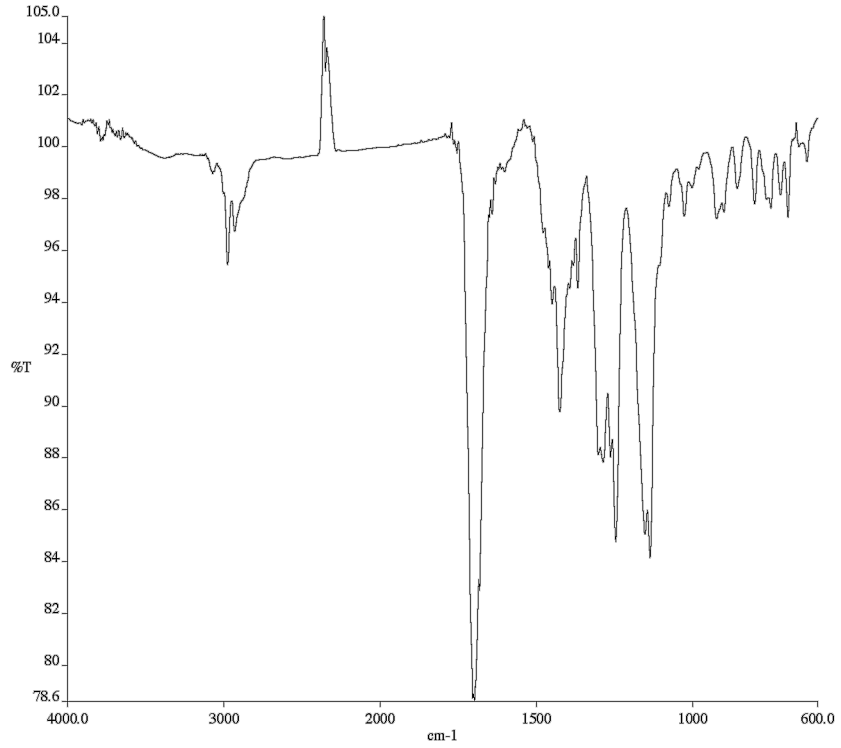
Infrared spectrum (Thin Film, NaCl) of compound **5i**.



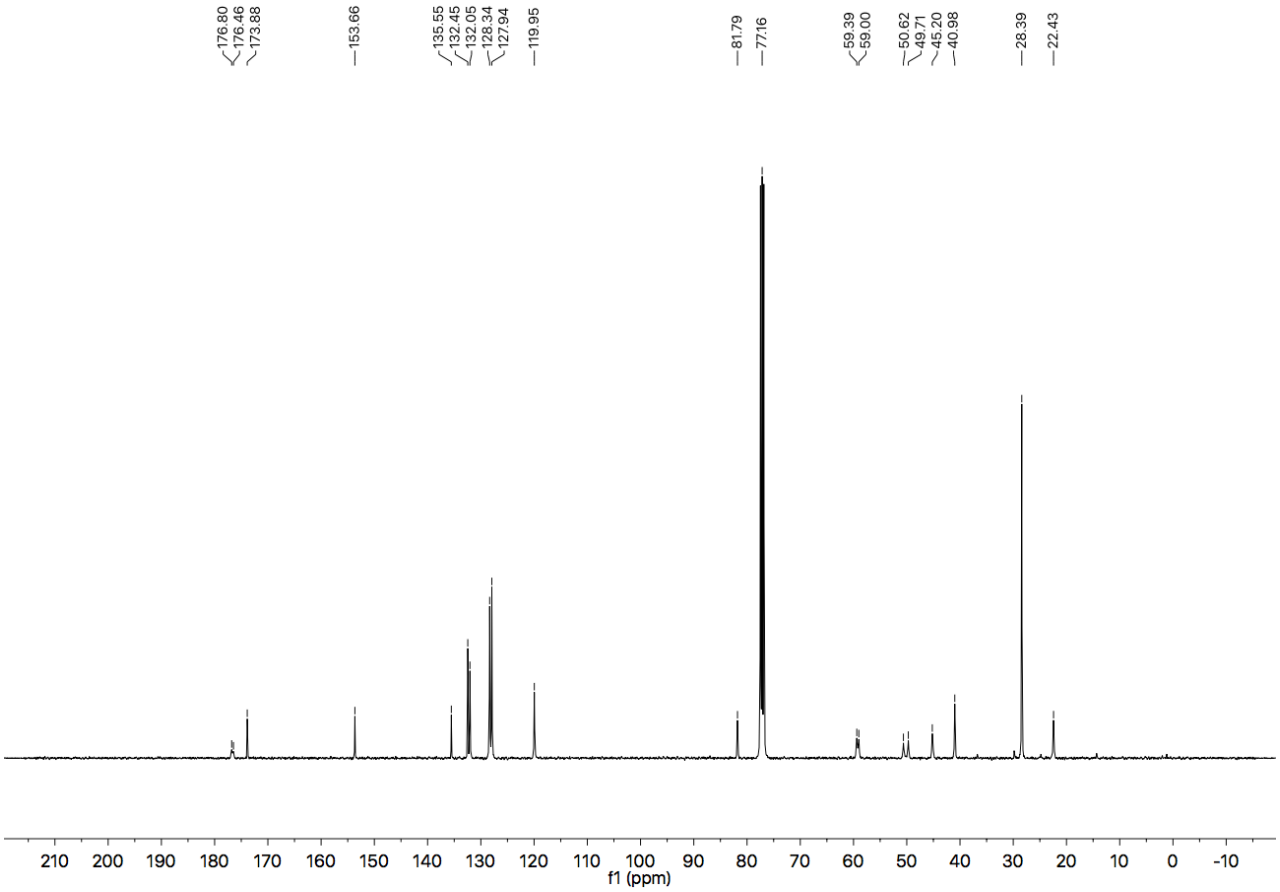
^{13}C NMR (101 MHz, $CDCl_3$) of compound **5i**.



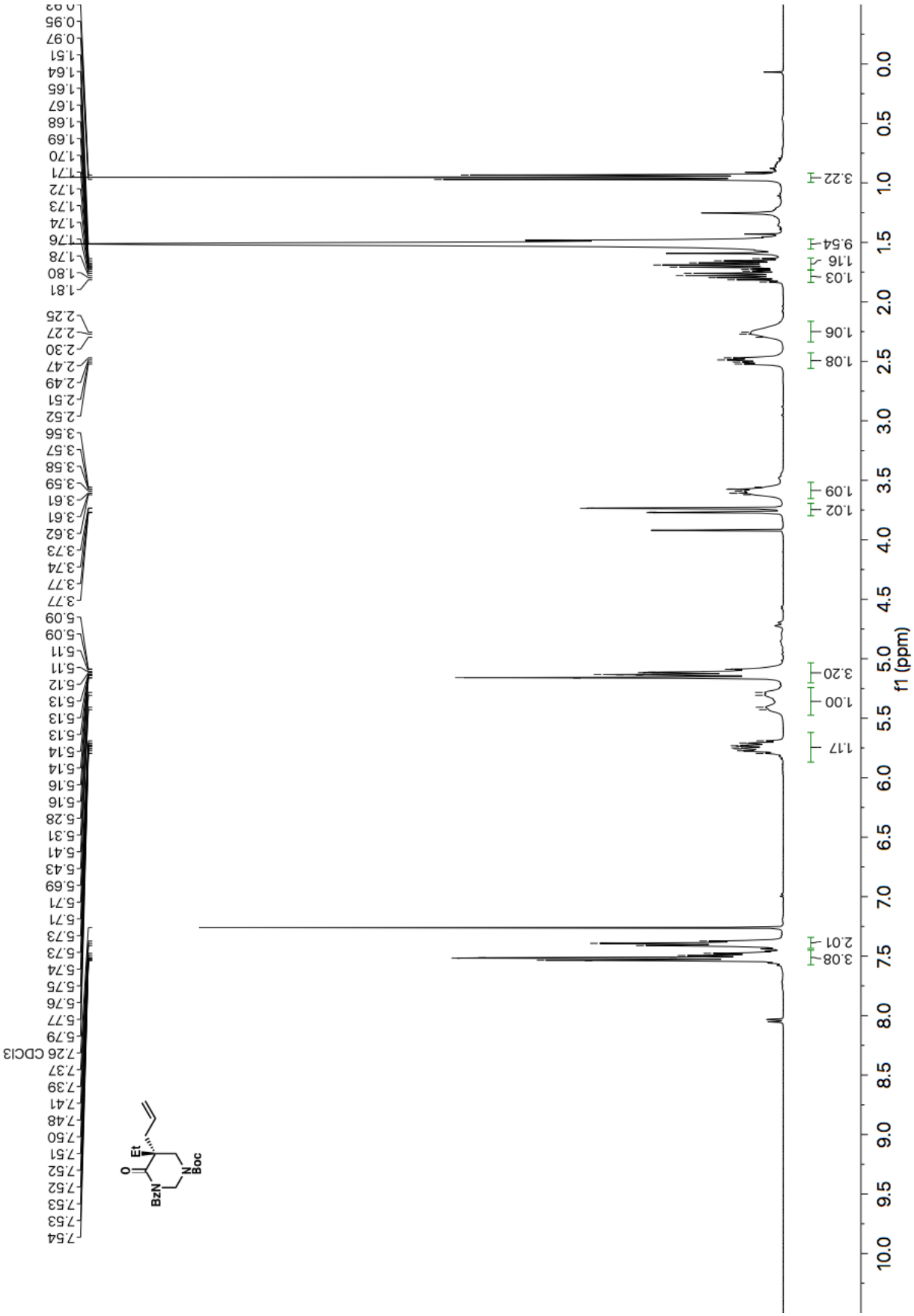
^{1}H NMR (500 MHz, $CDCl_3$) of compound **6a.**



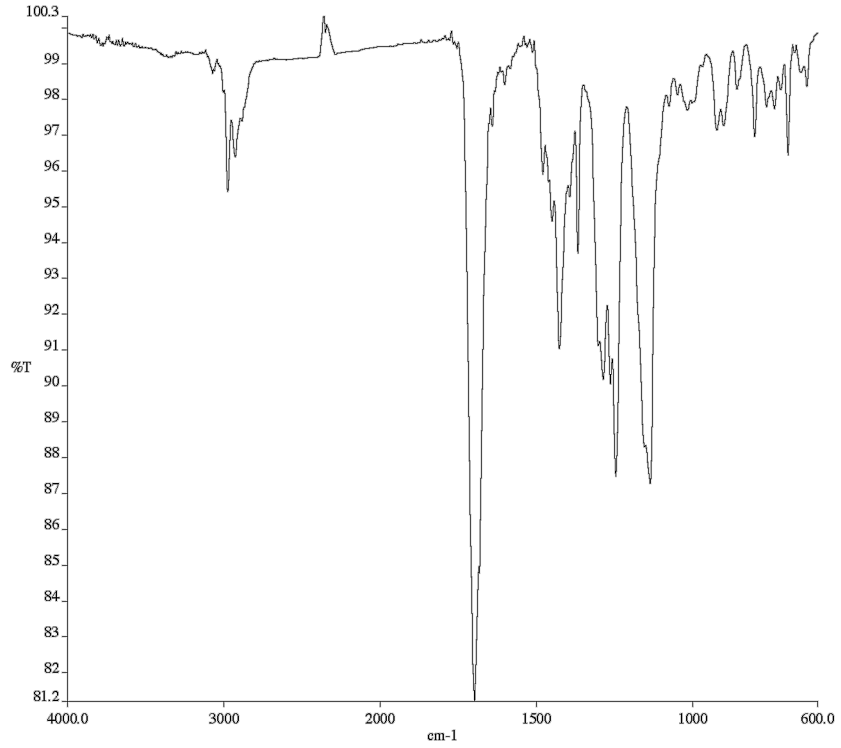
Infrared spectrum (Thin Film, NaCl) of compound **6a**.



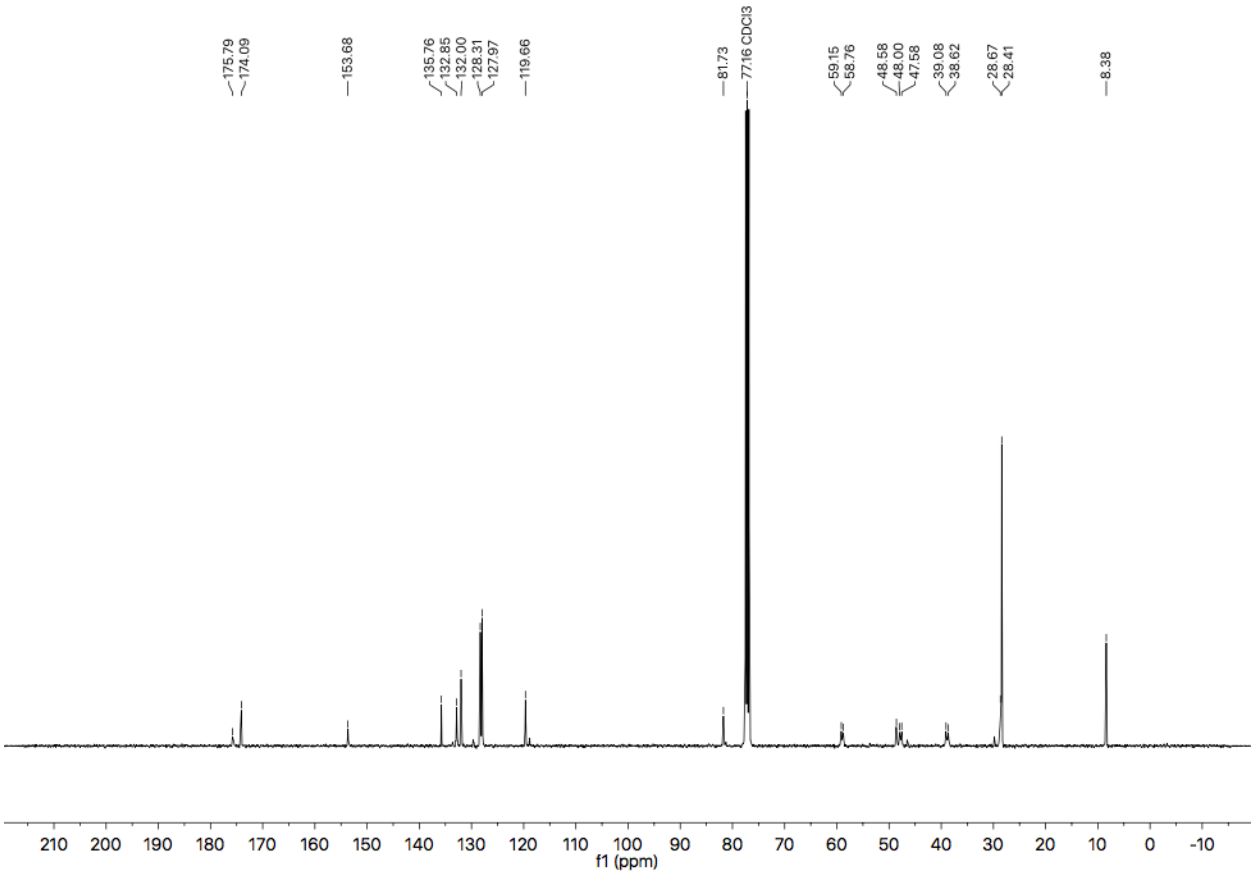
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6a**.



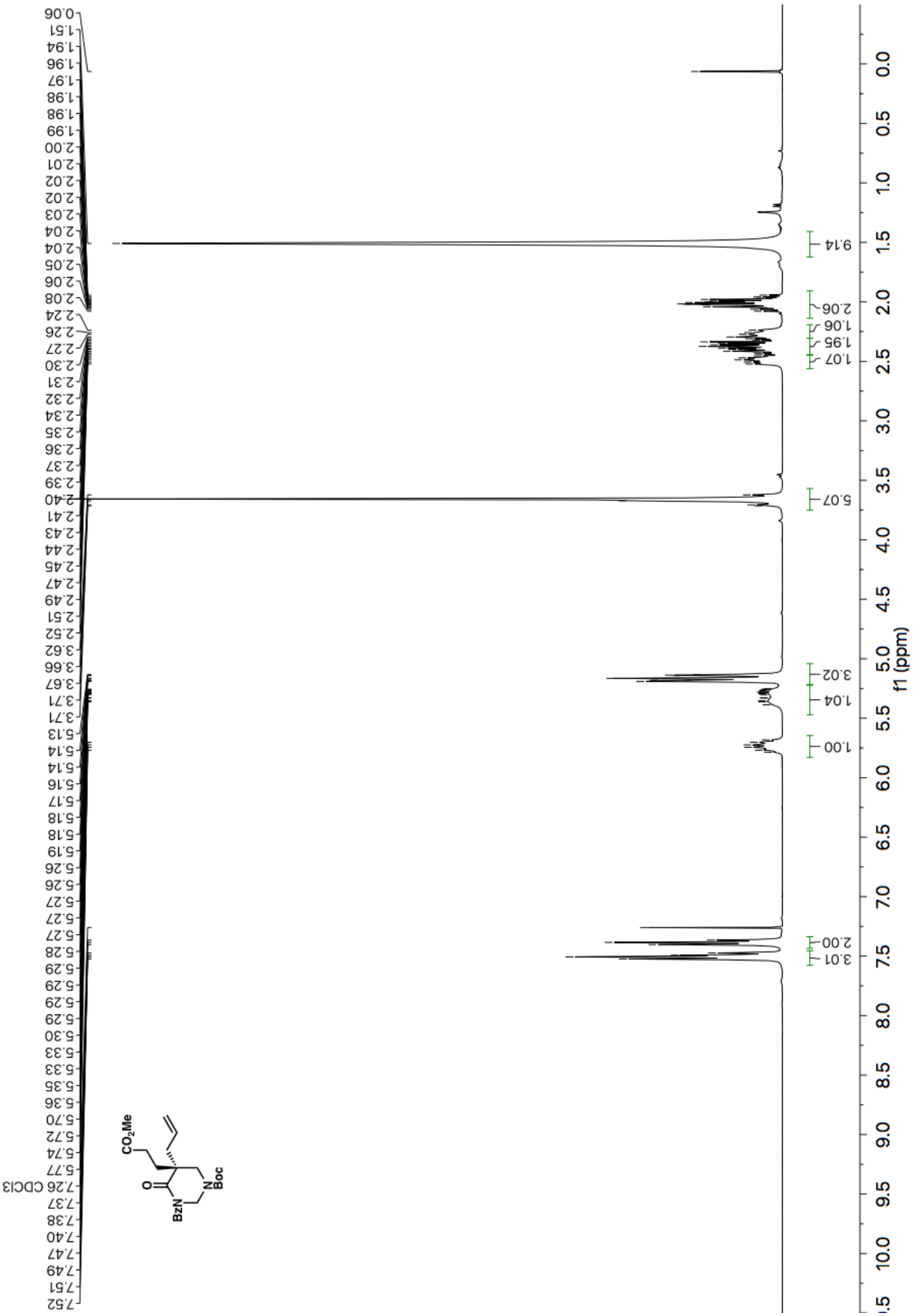
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6b.**



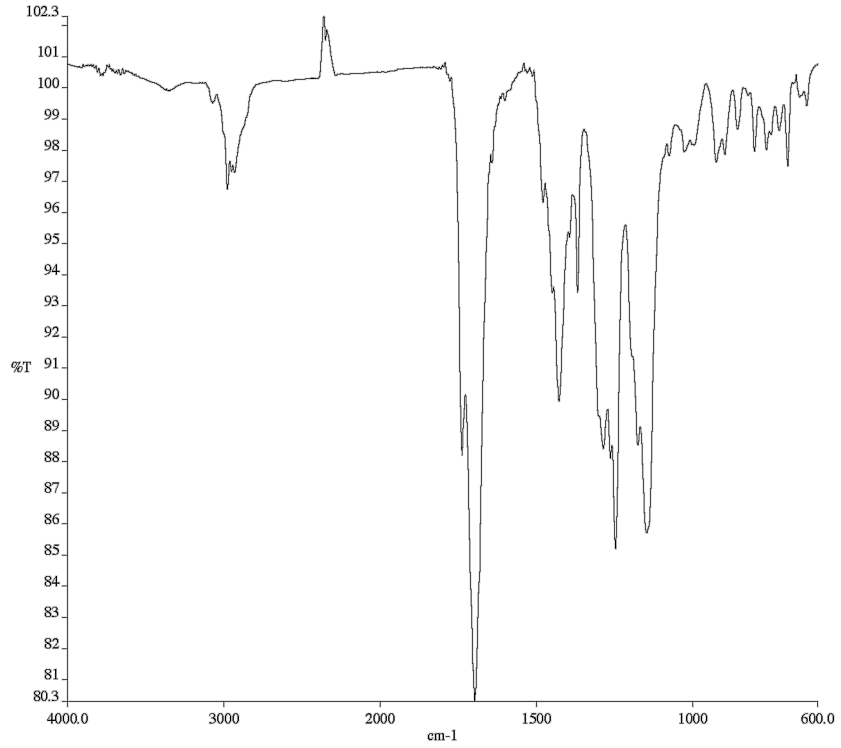
Infrared spectrum (Thin Film, NaCl) of compound **6b**.



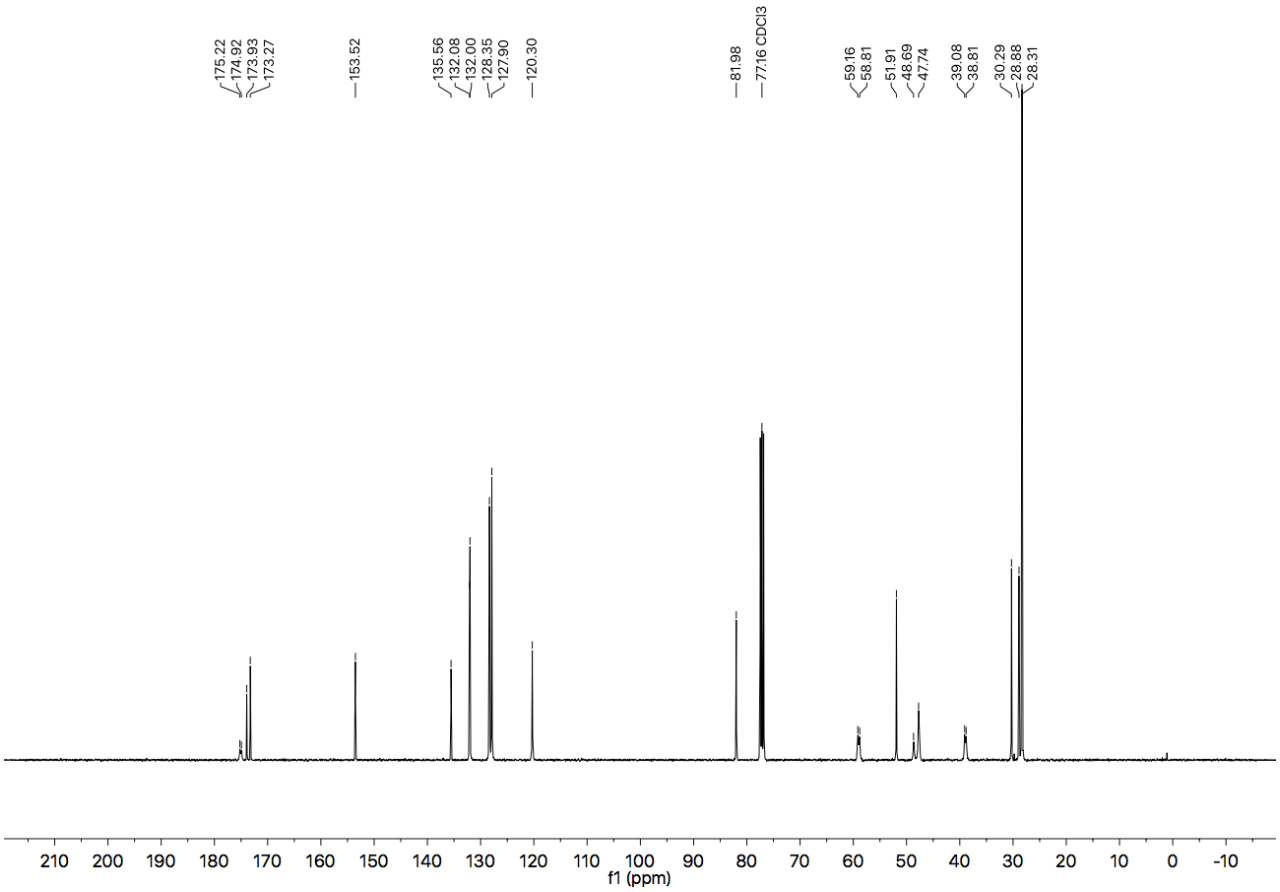
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6b**.



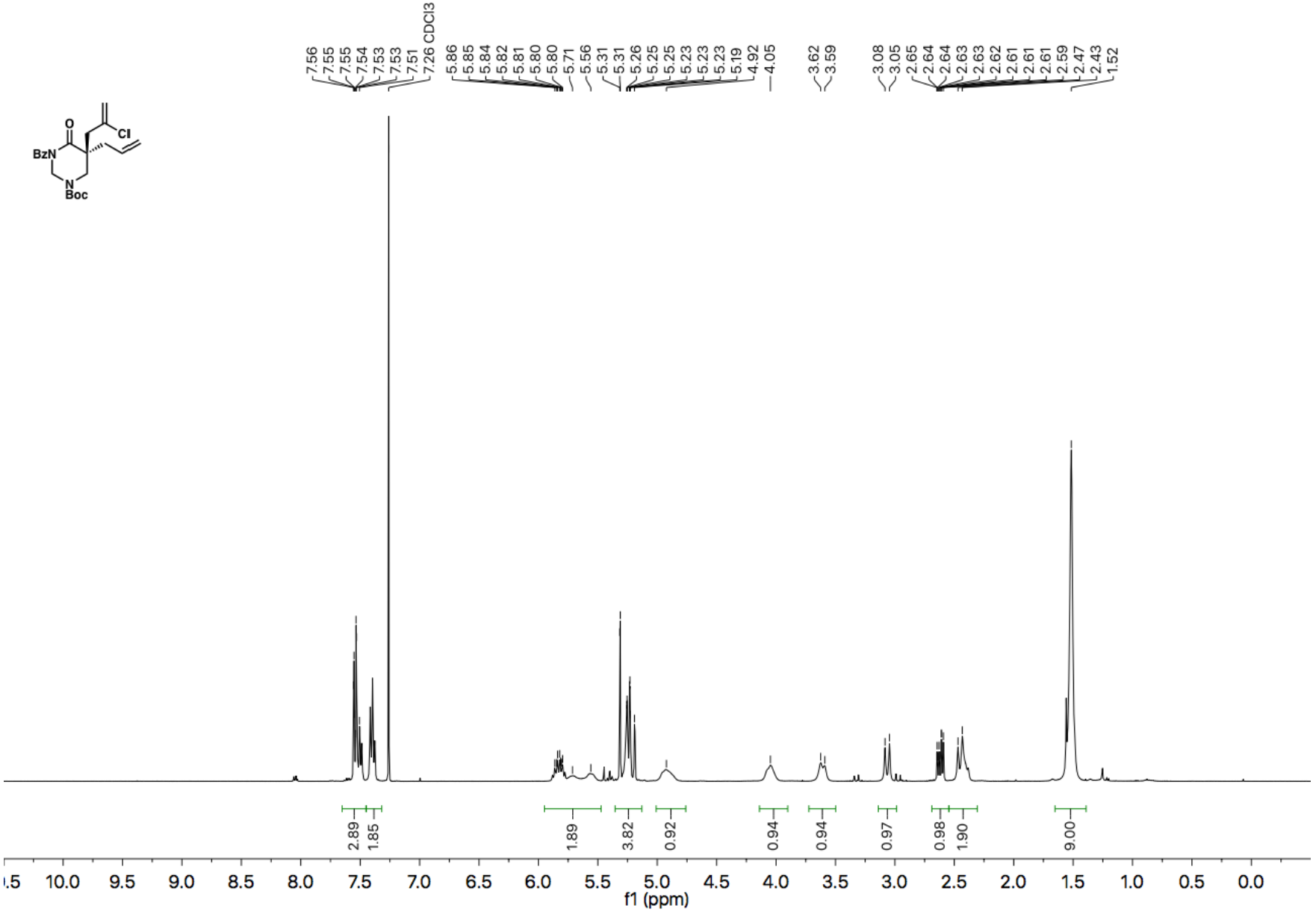
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6c.**



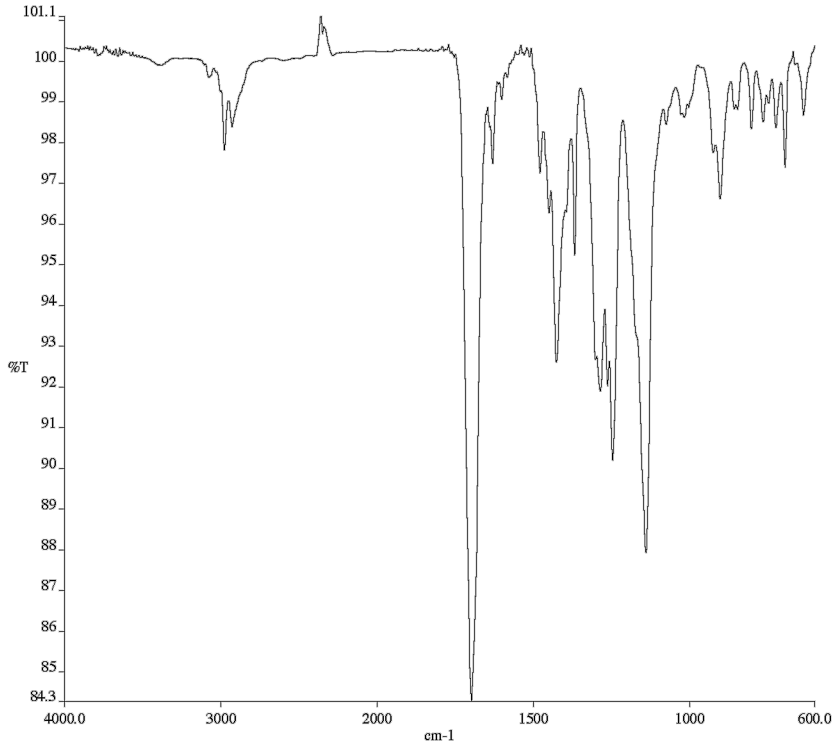
Infrared spectrum (Thin Film, NaCl) of compound **6c**.



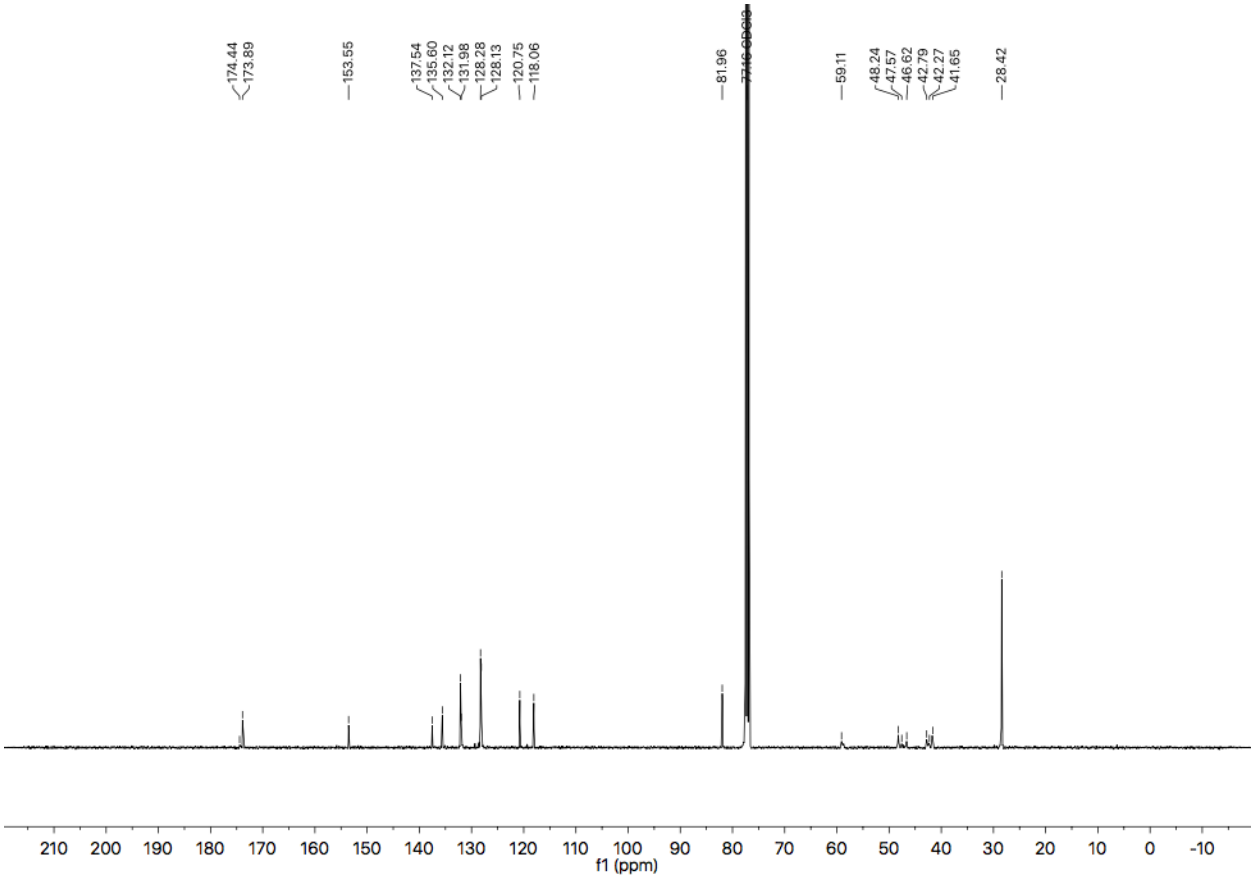
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6c**.



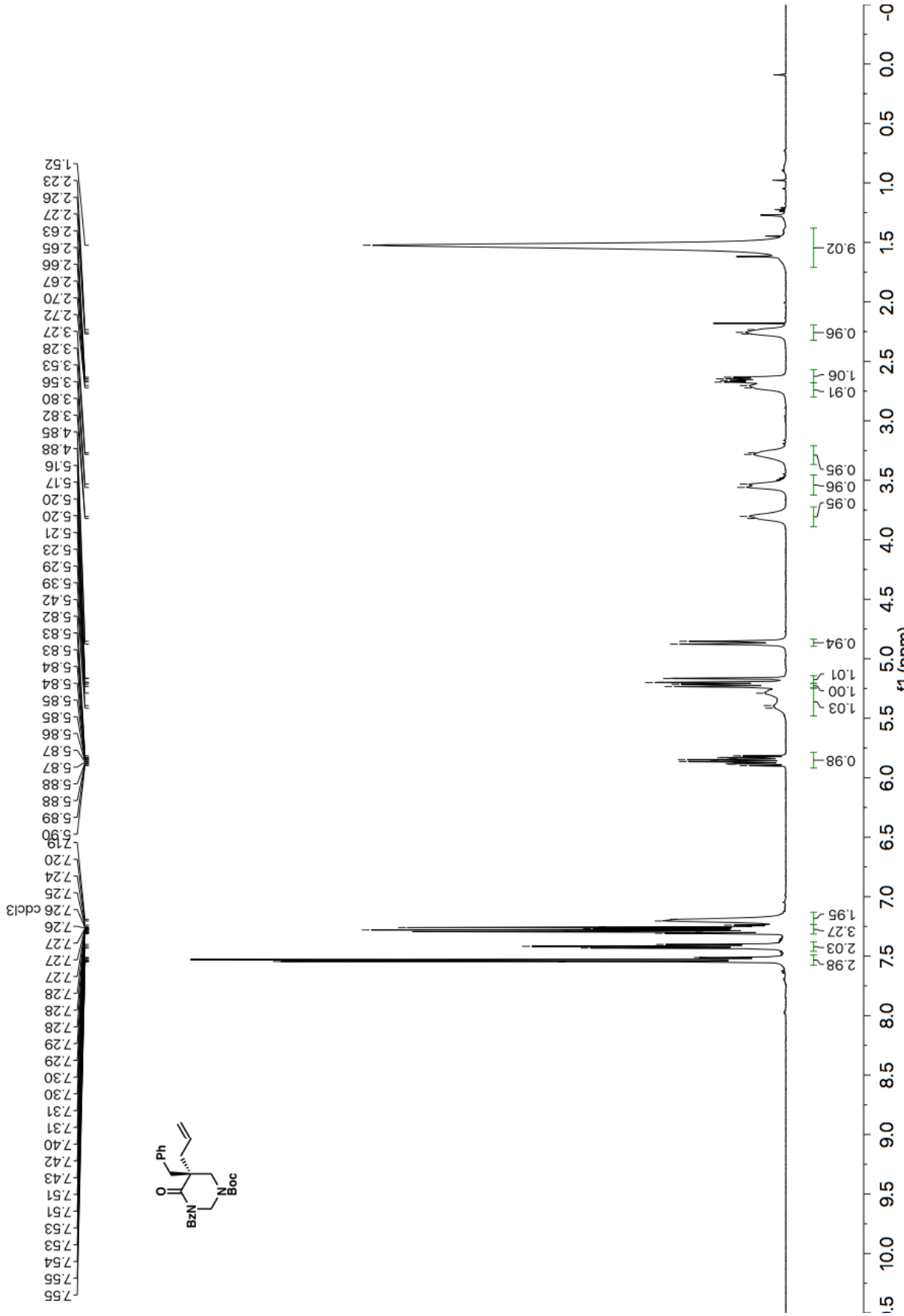
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6d.**



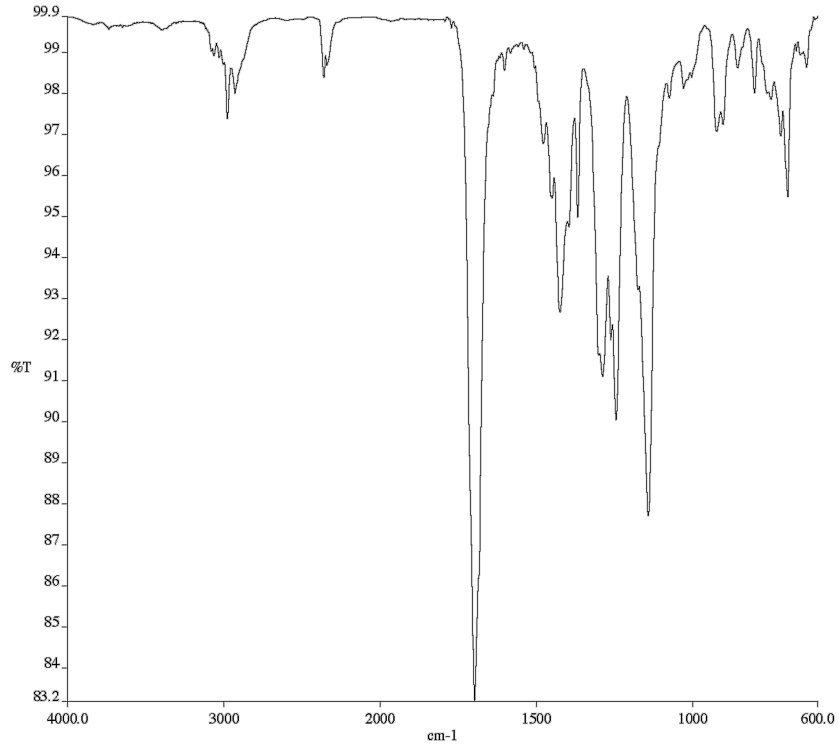
Infrared spectrum (Thin Film, NaCl) of compound **6d**.



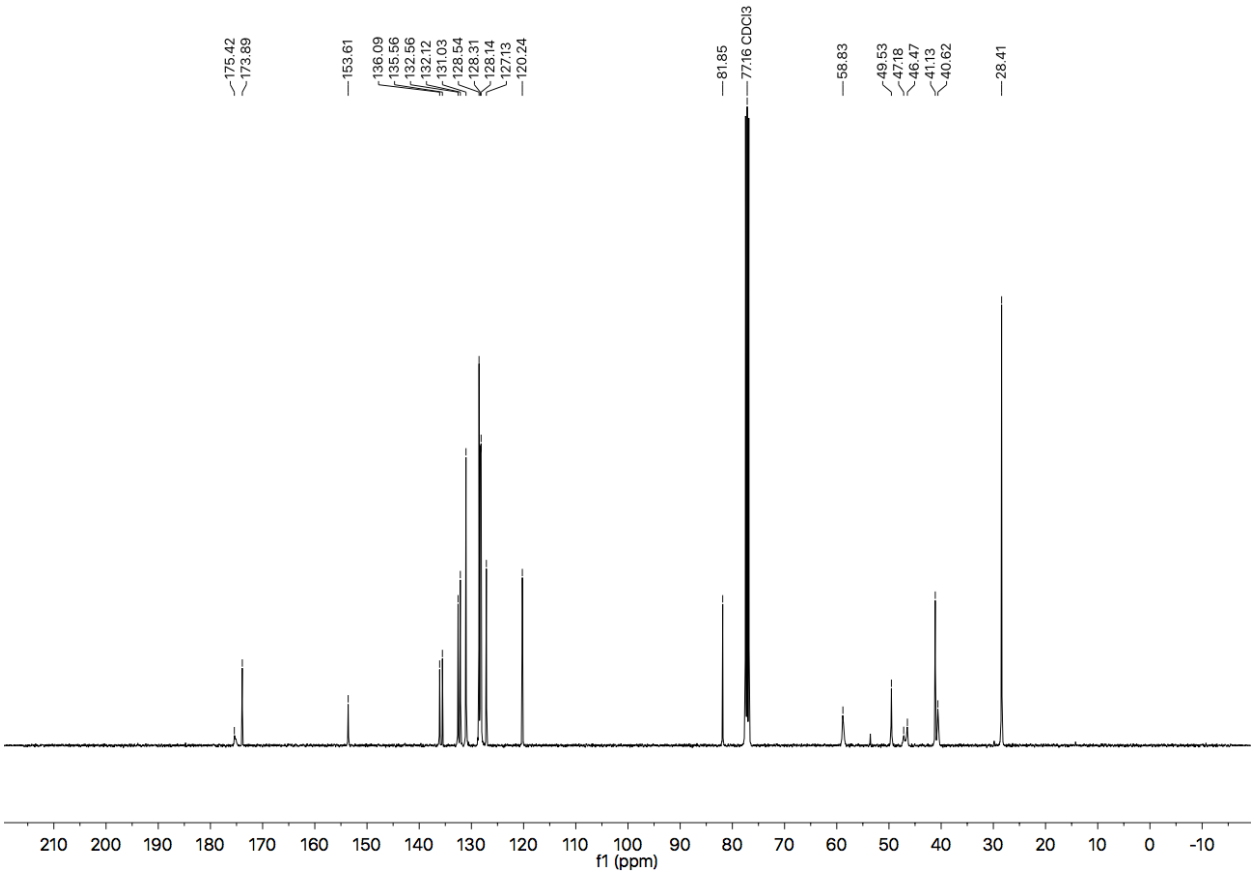
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6d**.



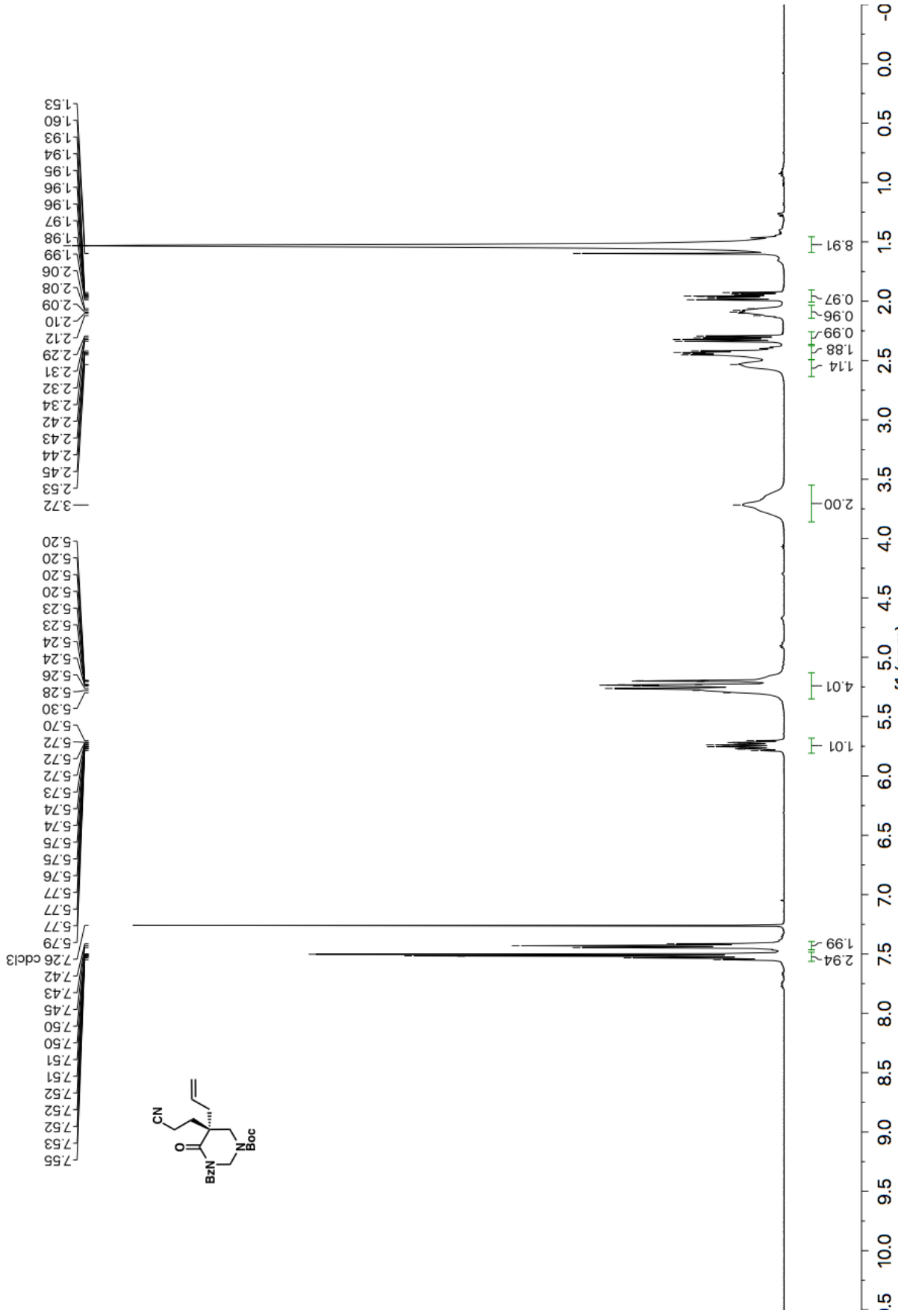
^{1}H NMR (500 MHz, $CDCl_3$) of compound **6e.**



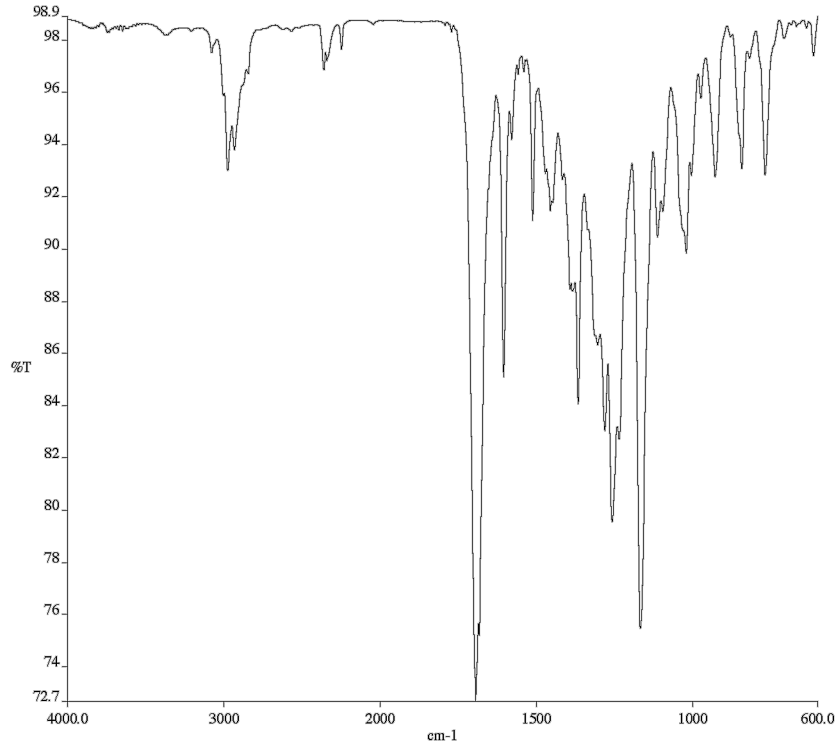
Infrared spectrum (Thin Film, NaCl) of compound **6e**.



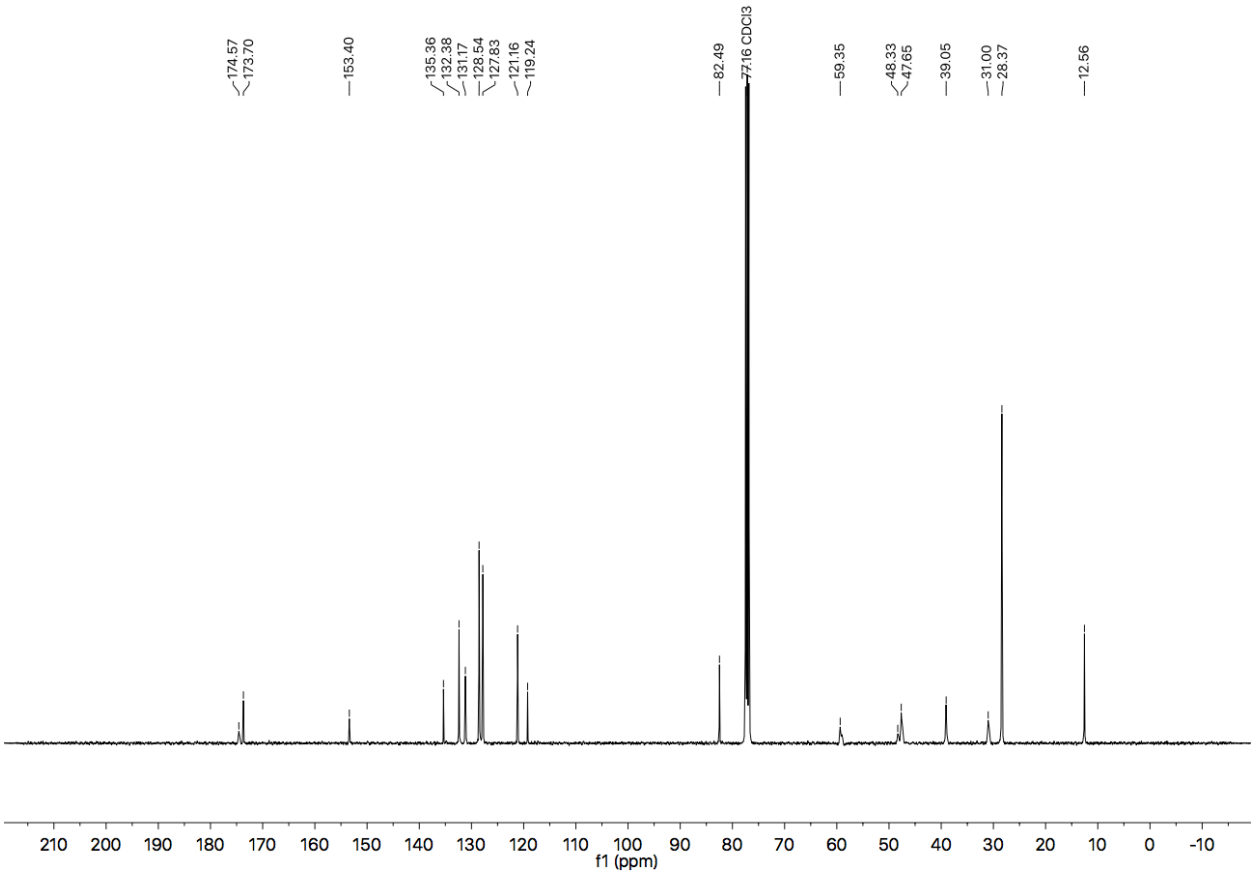
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6e**.



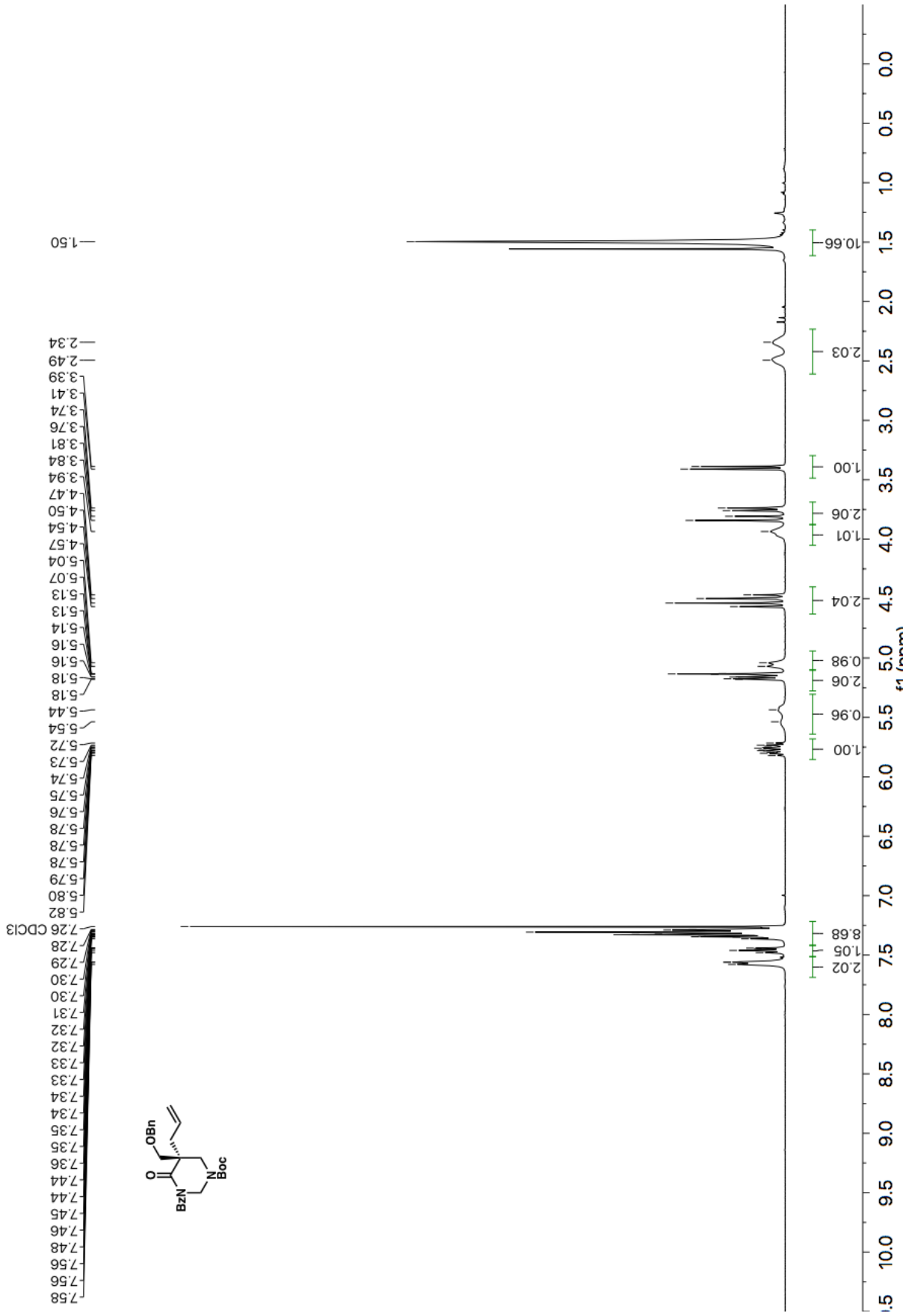
^{1}H NMR (500 MHz, $CDCl_3$) of compound **6f.**



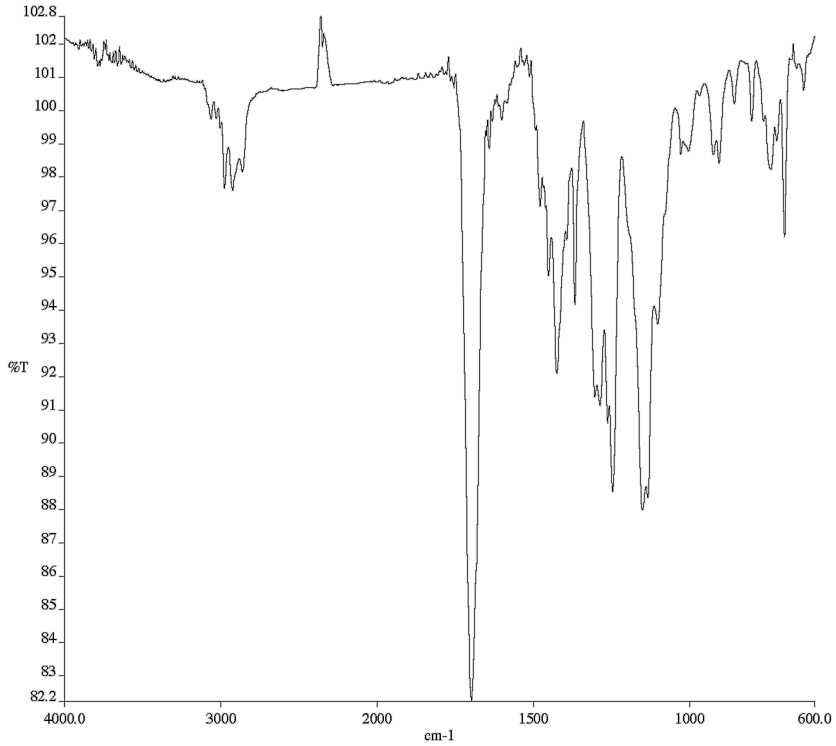
Infrared spectrum (Thin Film, NaCl) of compound **6f**.



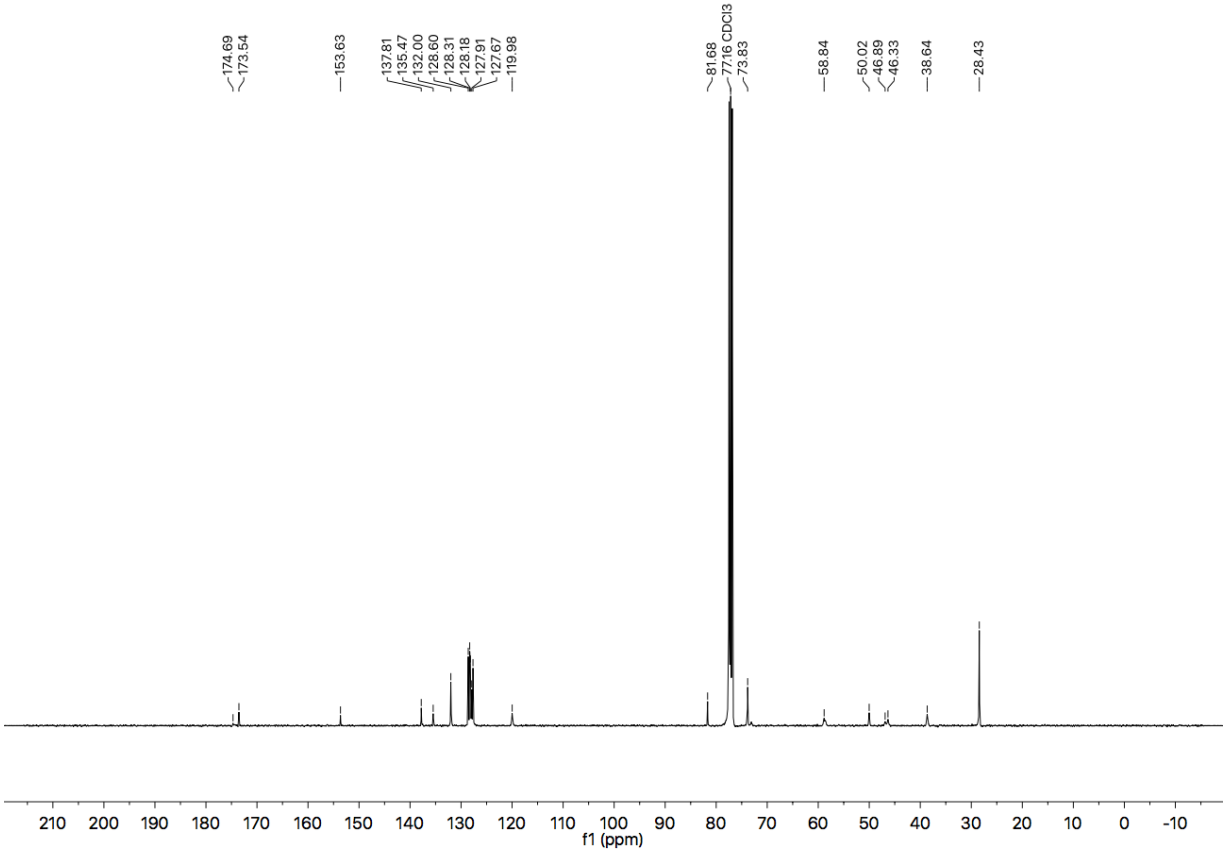
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6f**.



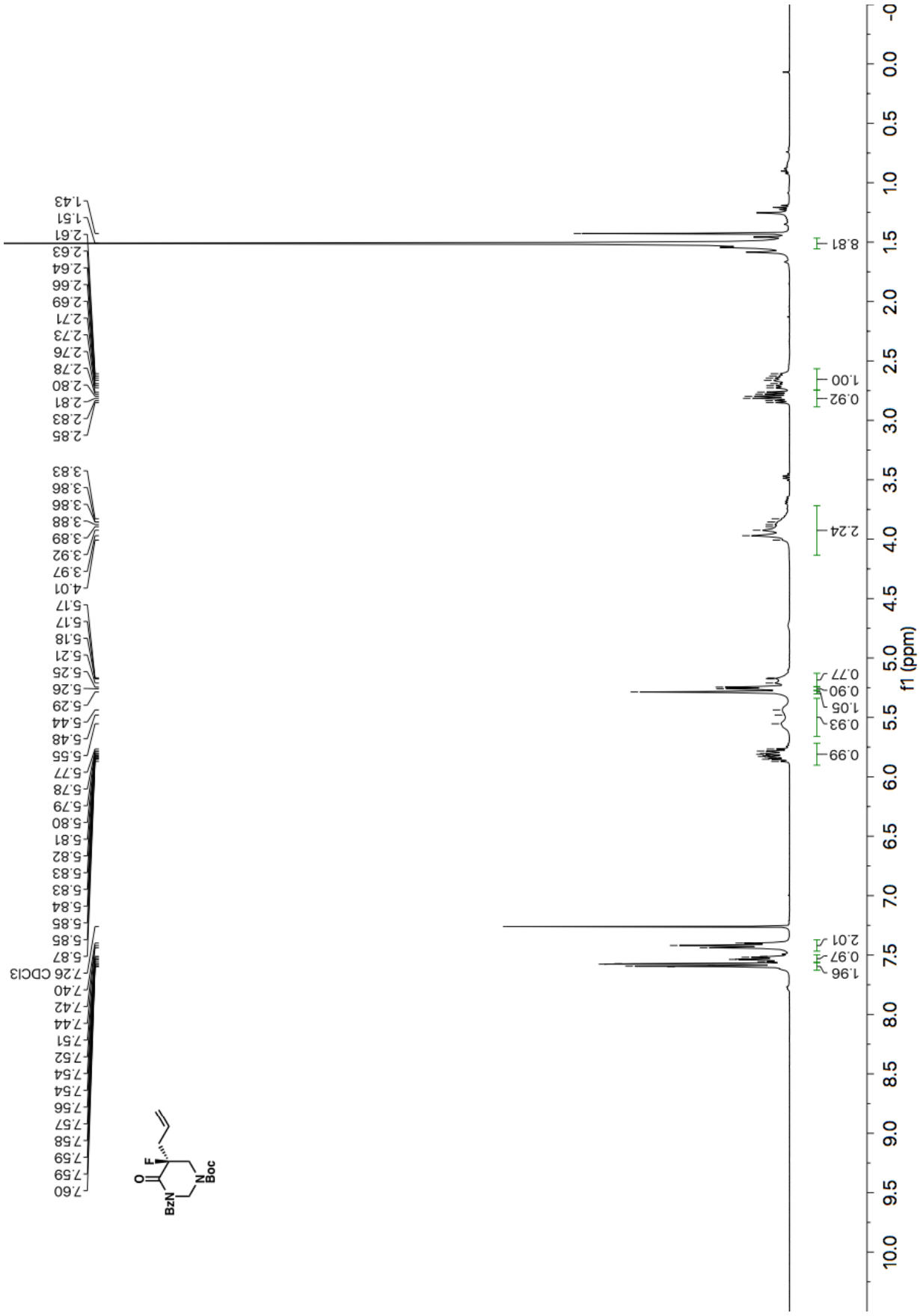
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6g.**



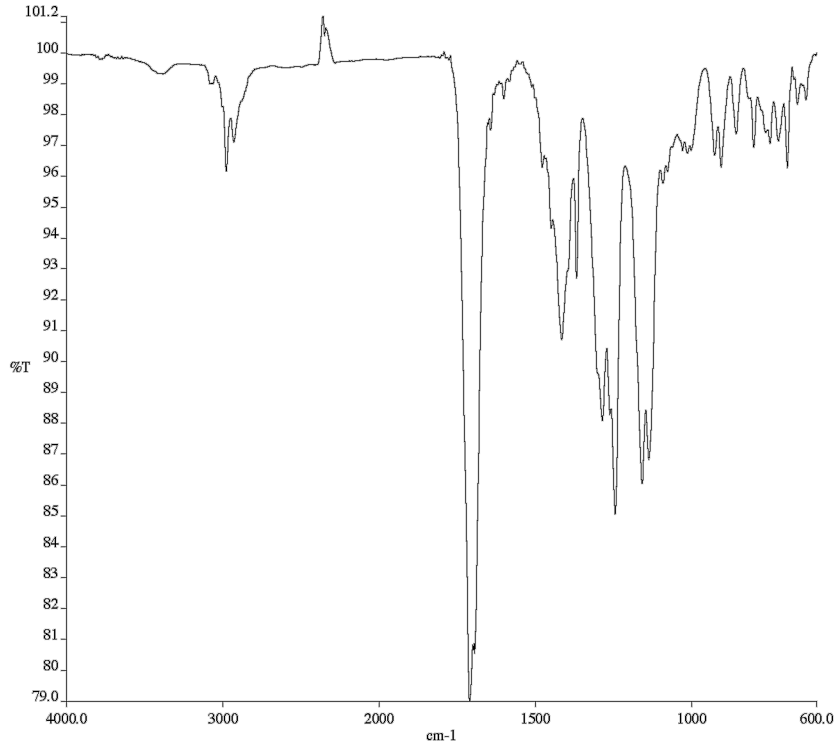
Infrared spectrum (Thin Film, NaCl) of compound **6g**.



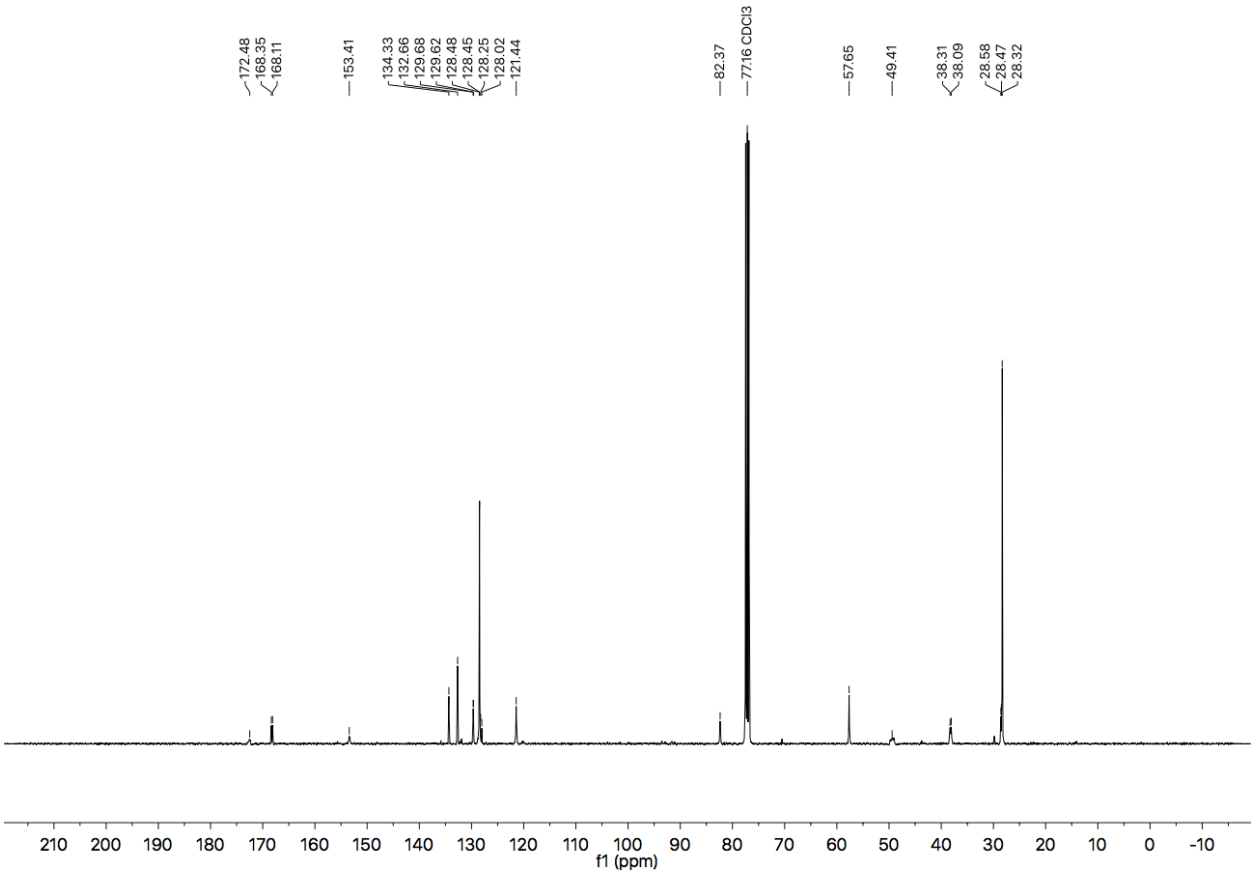
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6g**.



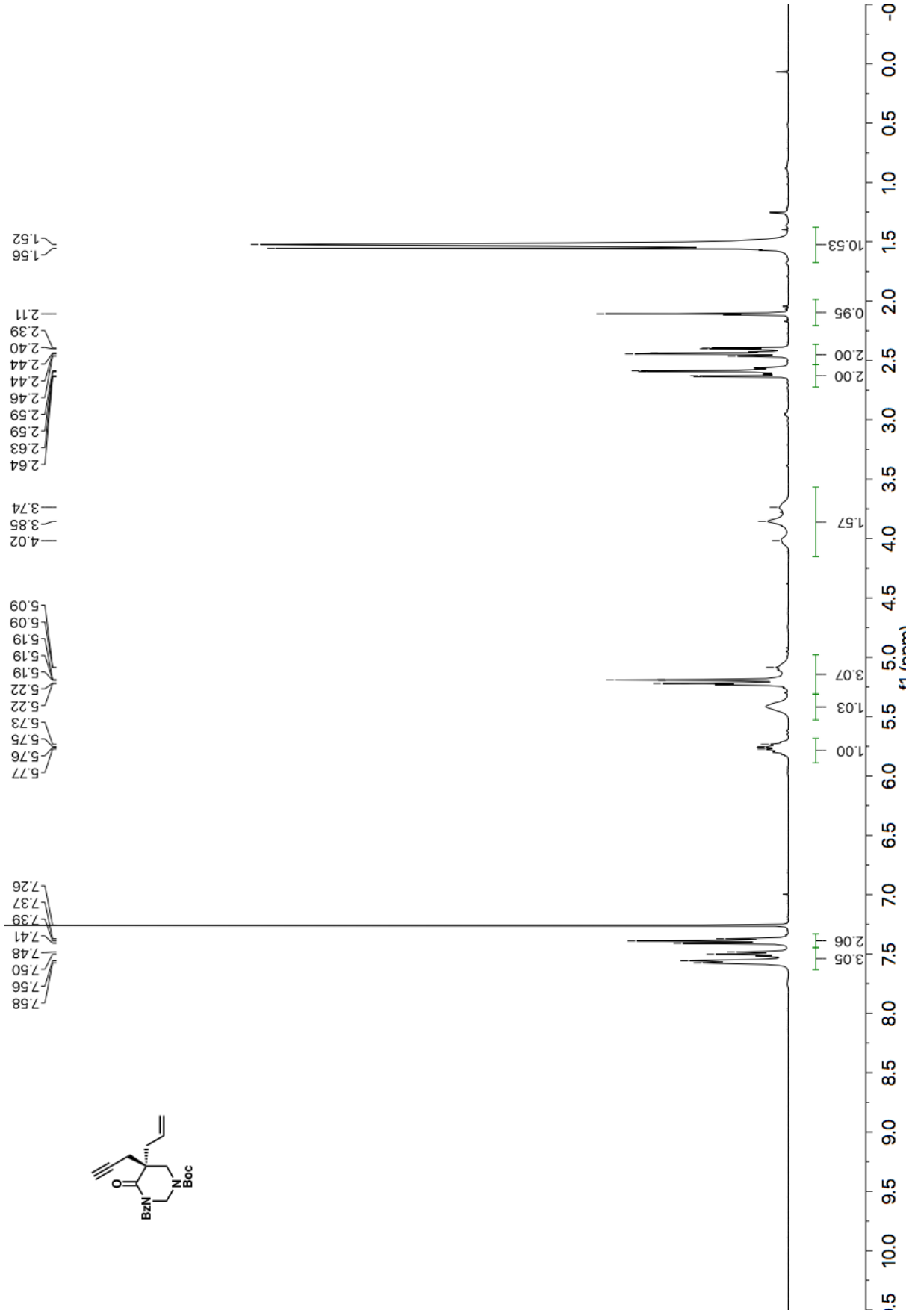
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6h.**



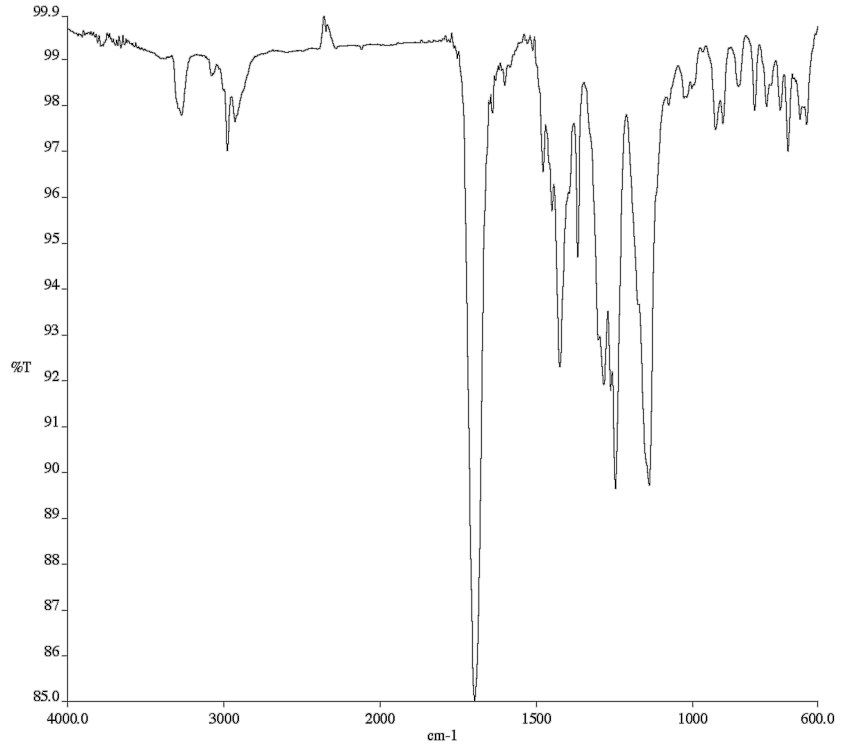
Infrared spectrum (Thin Film, NaCl) of compound **6h**.



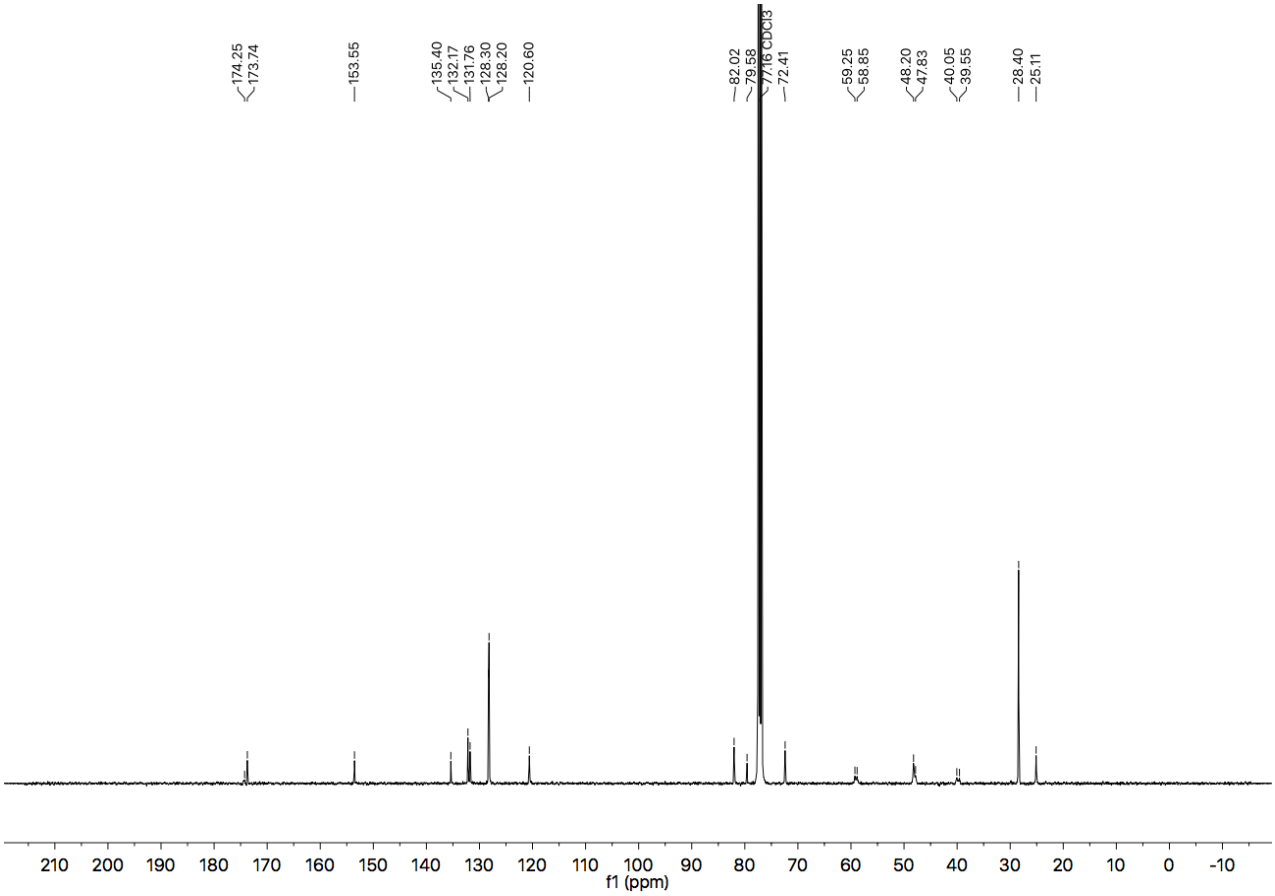
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6h**.



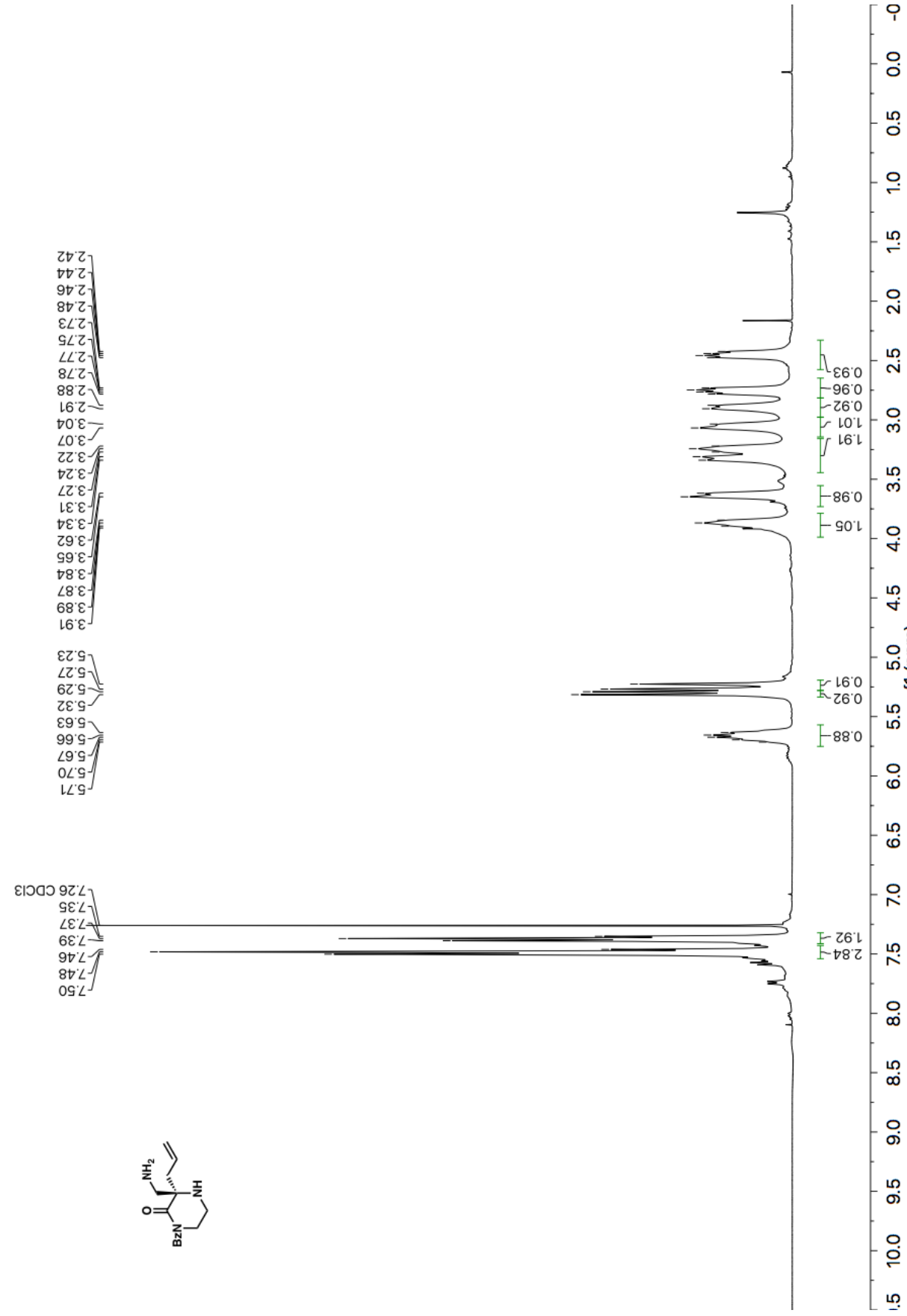
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6i.**



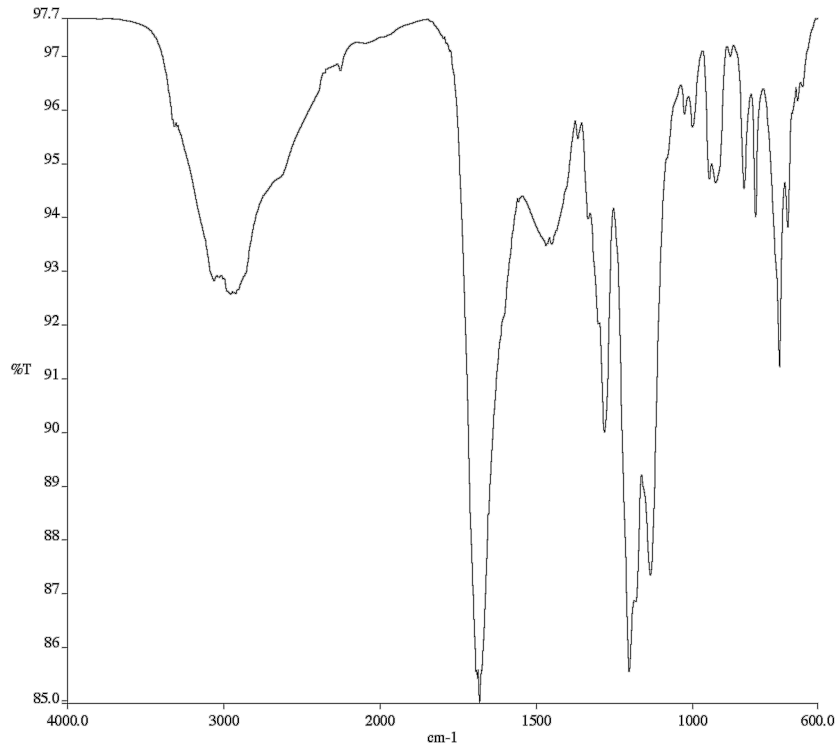
Infrared spectrum (Thin Film, NaCl) of compound **6i**.



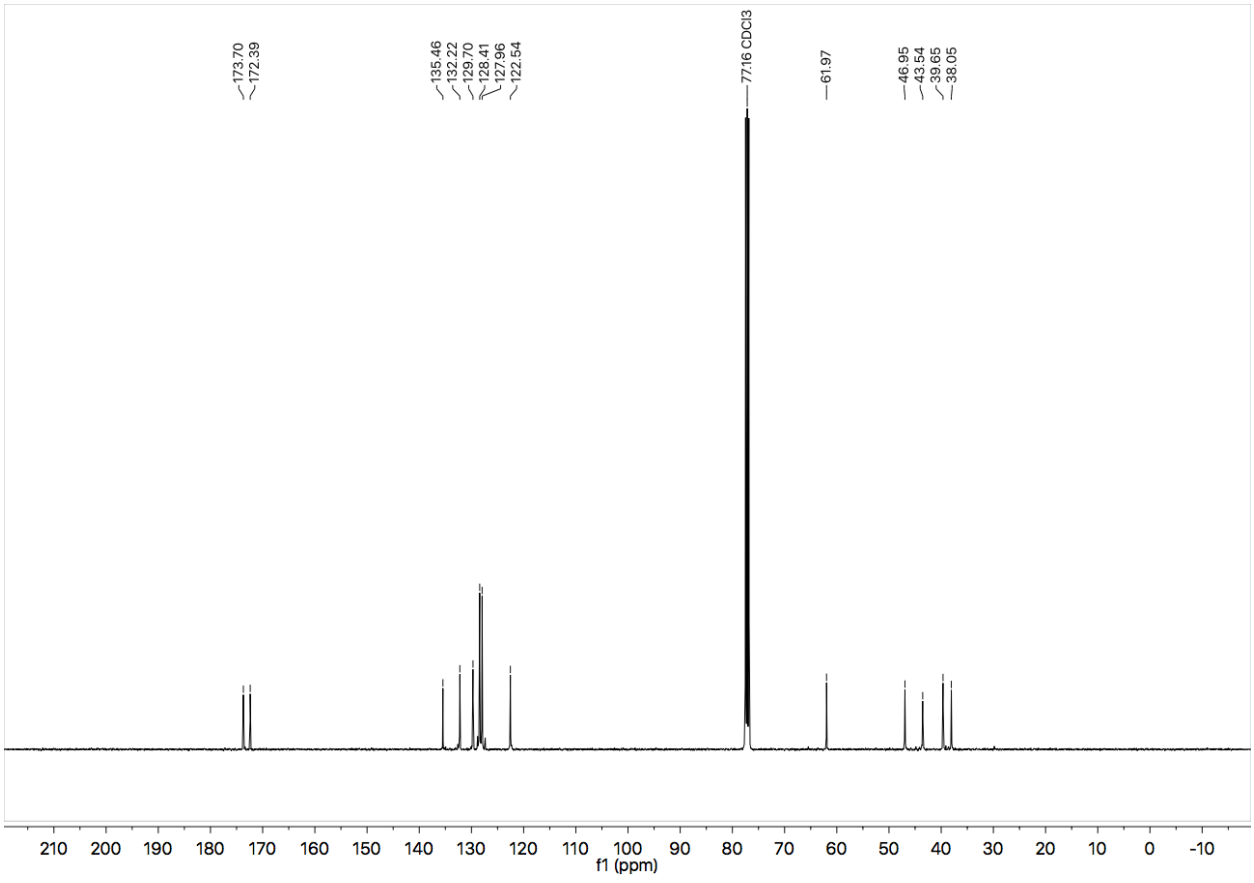
^{13}C NMR (101 MHz, $CDCl_3$) of compound **6i**.



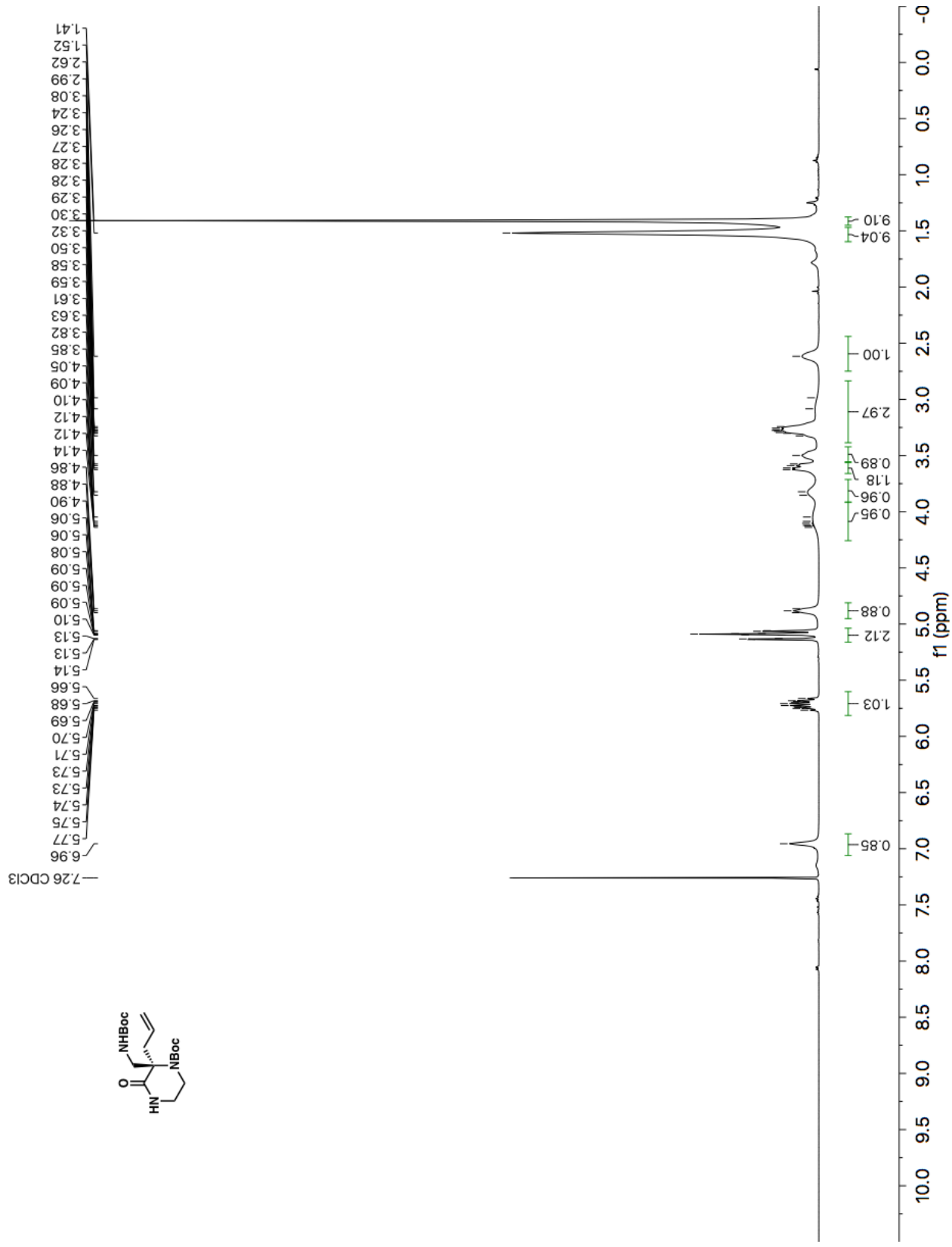
^{1}H NMR (400 MHz, $CDCl_3$) of compound **8.**



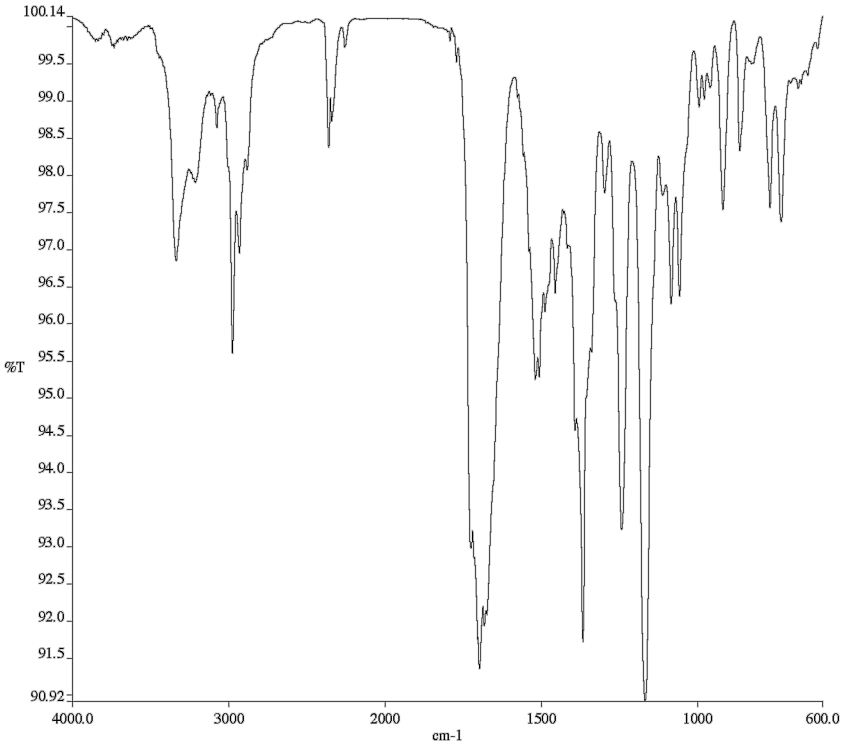
Infrared spectrum (Thin Film, NaCl) of compound **8**.



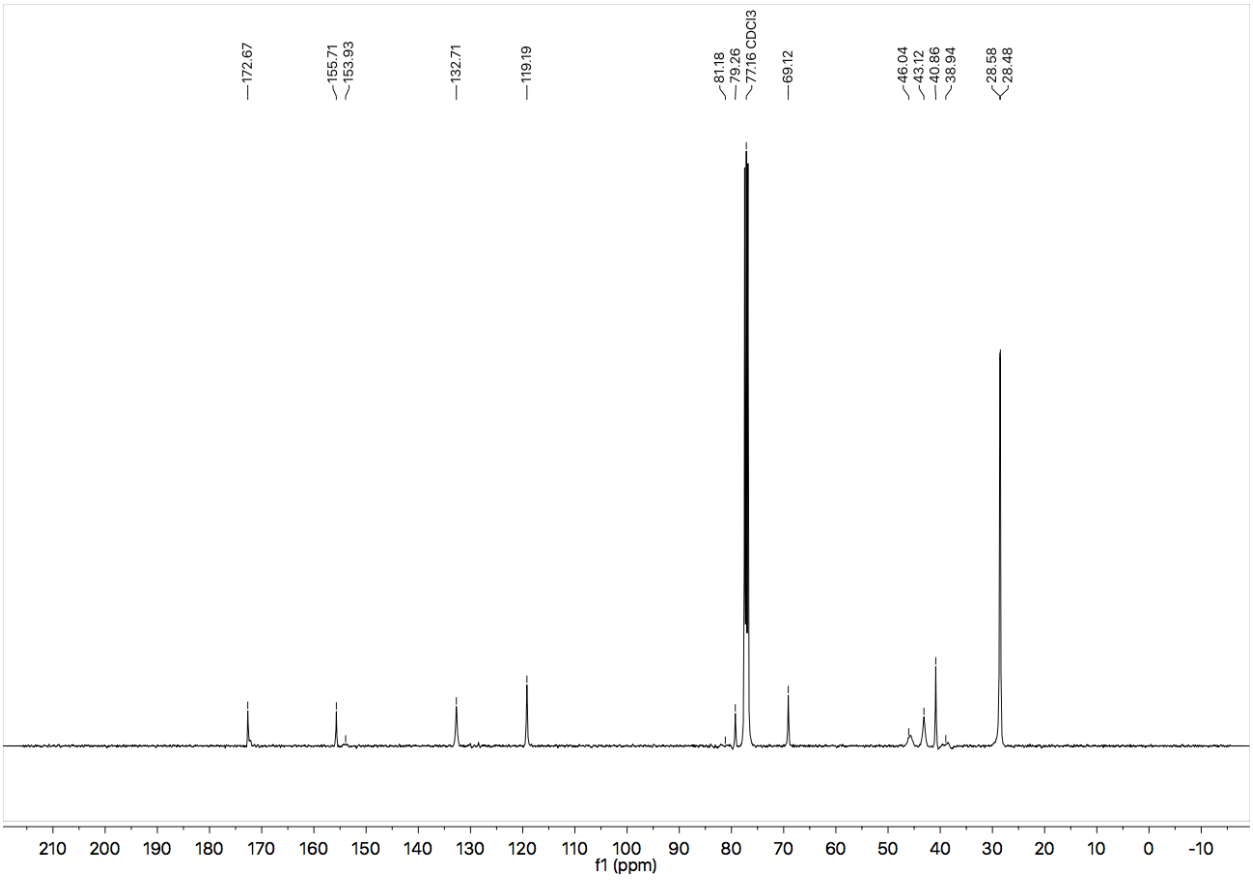
^{13}C NMR (101 MHz, $CDCl_3$) of compound **8**.



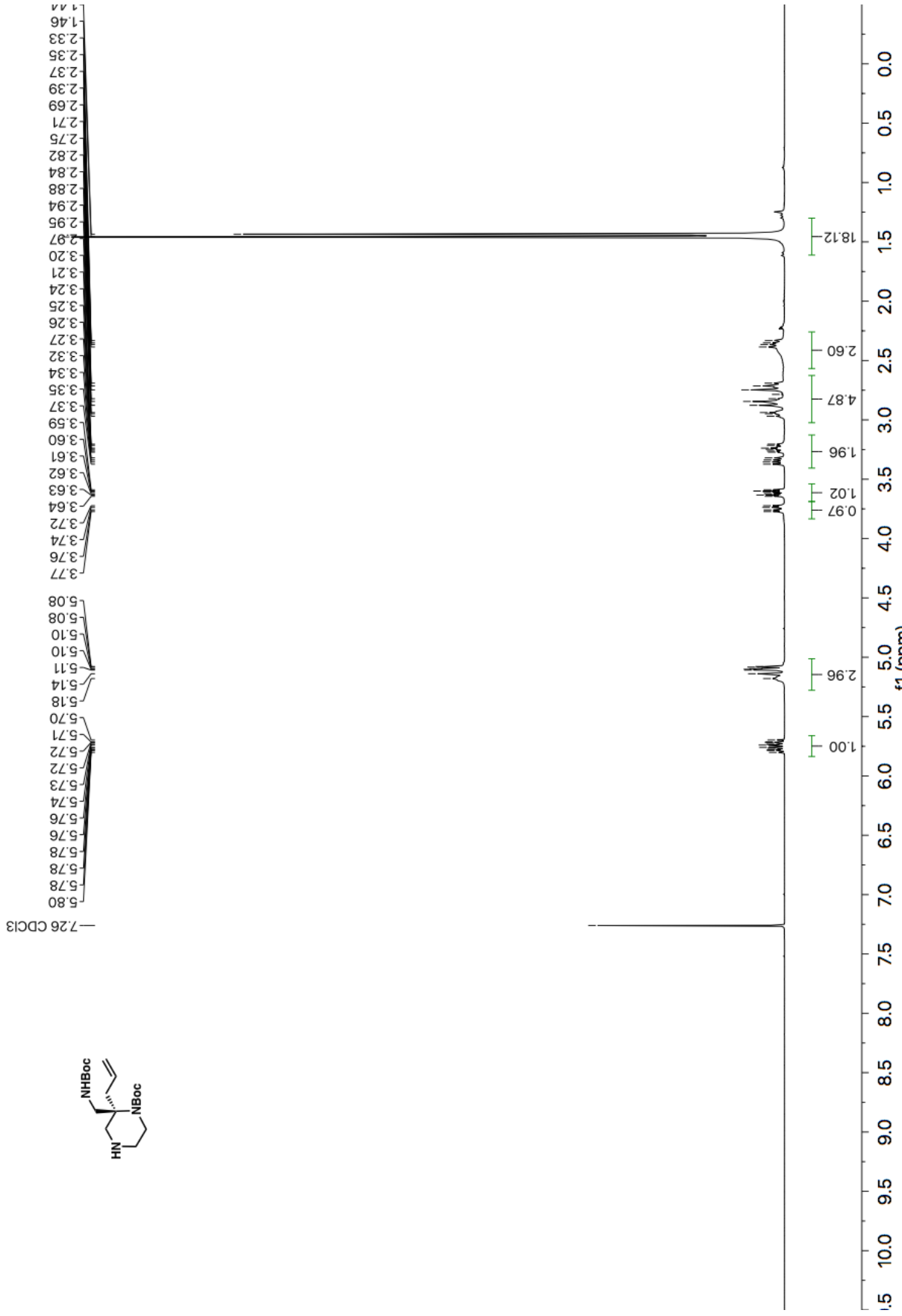
^{1}H NMR (400 MHz, $CDCl_3$) of compound **9.**



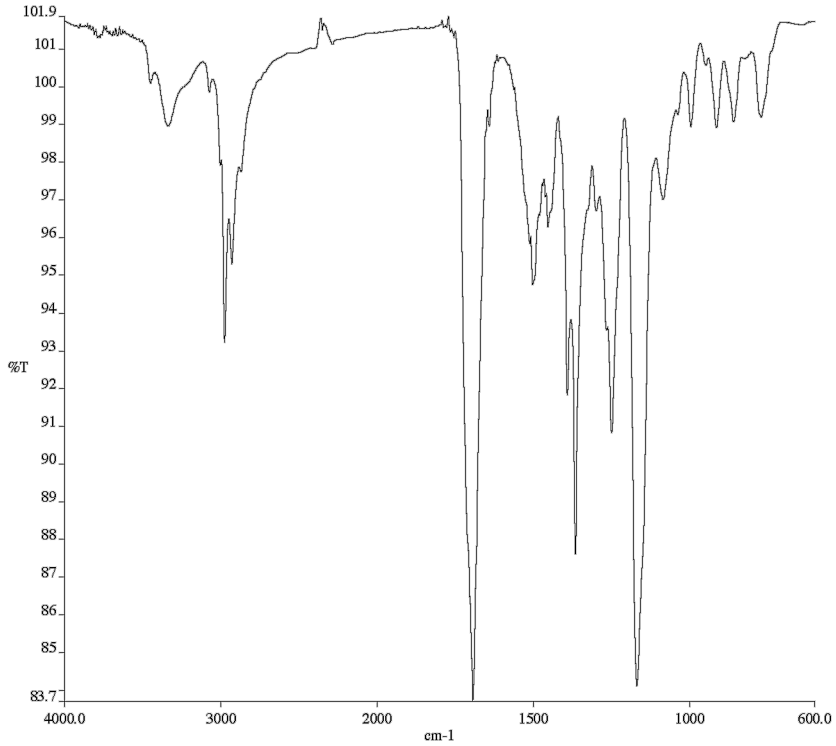
Infrared spectrum (Thin Film, NaCl) of compound **9**.



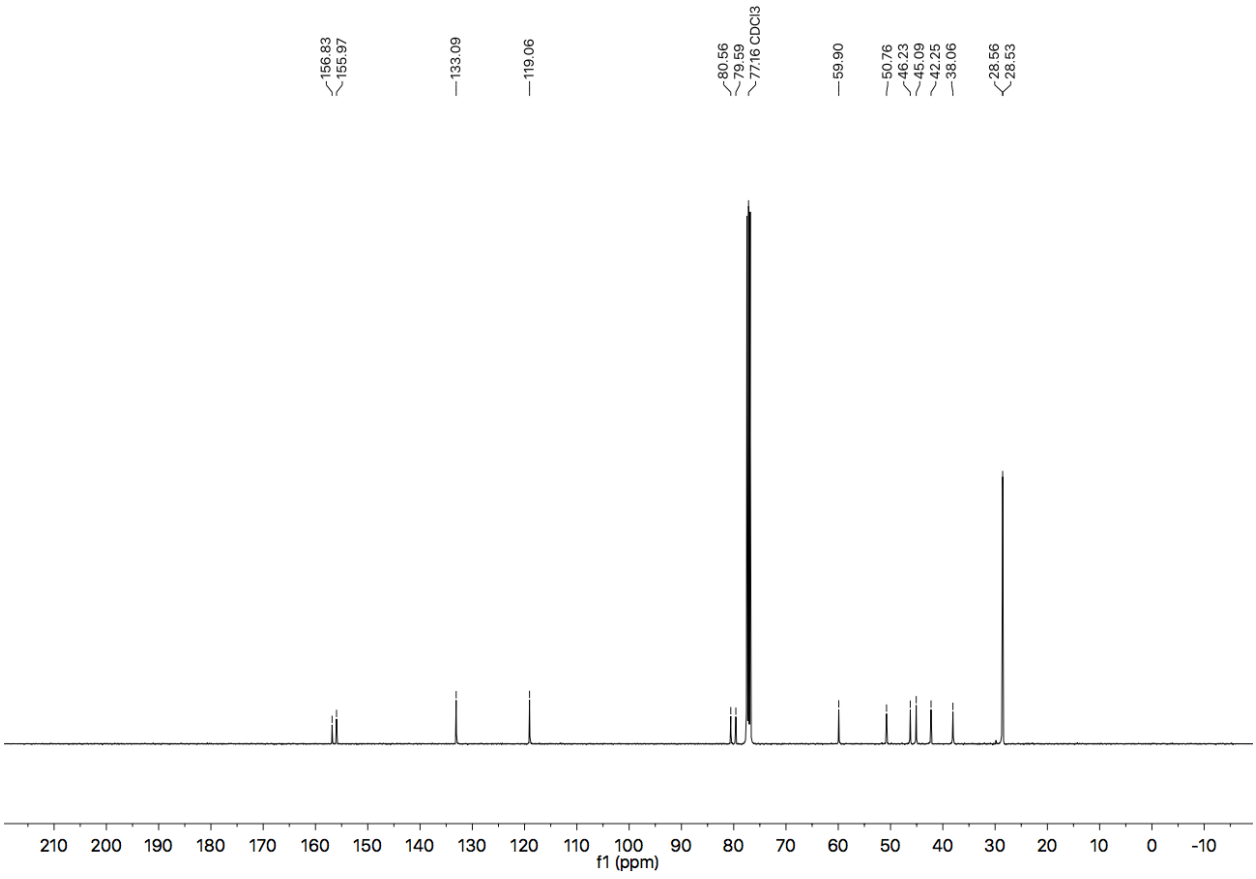
^{13}C NMR (101 MHz, $CDCl_3$) of compound **9**.



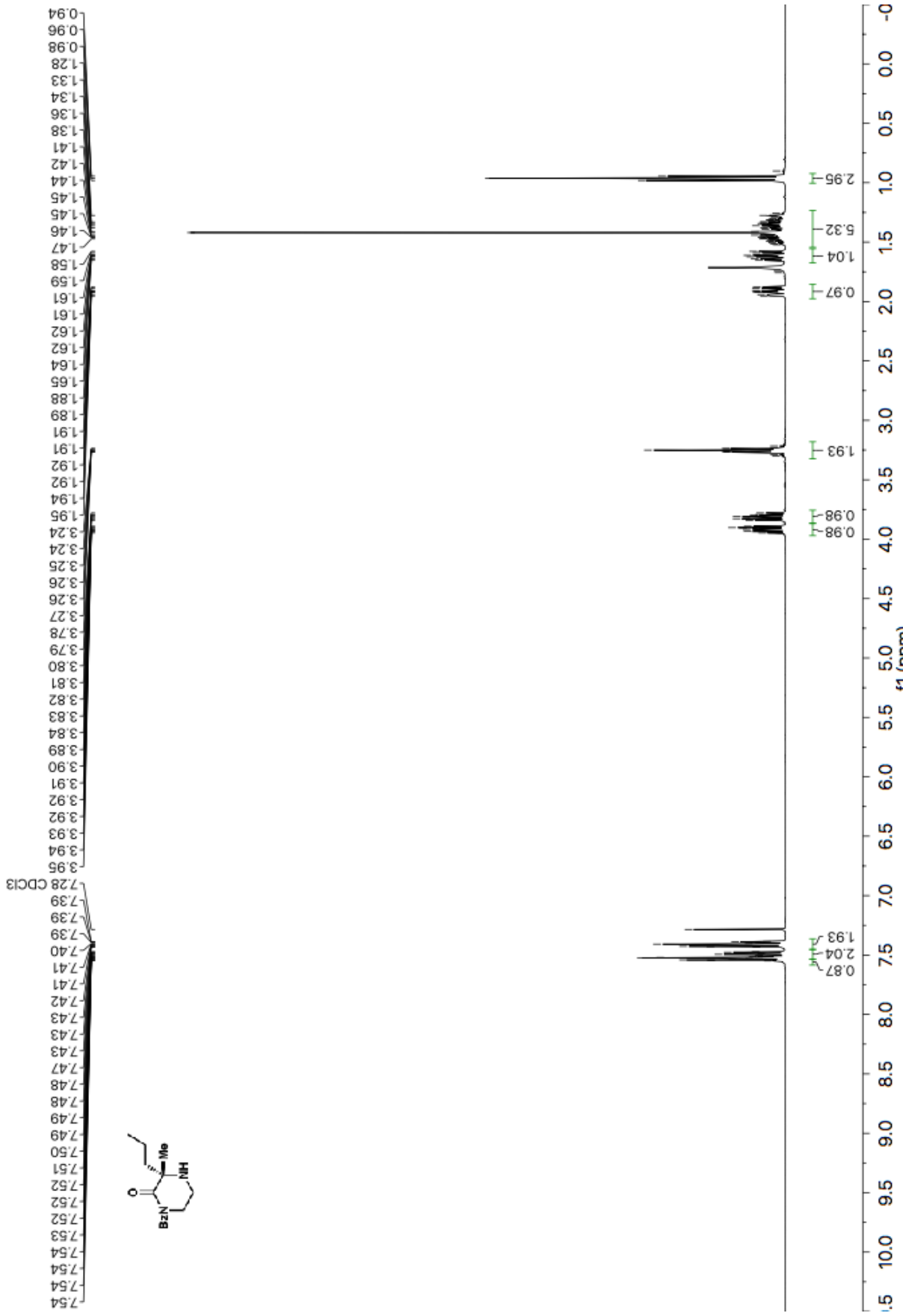
^{1}H NMR (400 MHz, $CDCl_3$) of compound **10.**



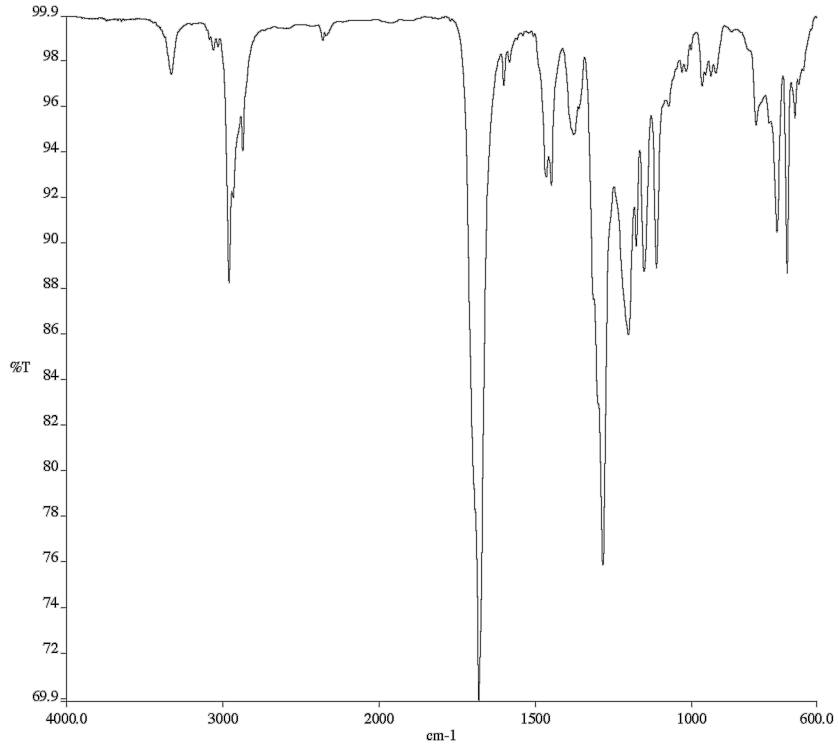
Infrared spectrum (Thin Film, NaCl) of compound **10**.



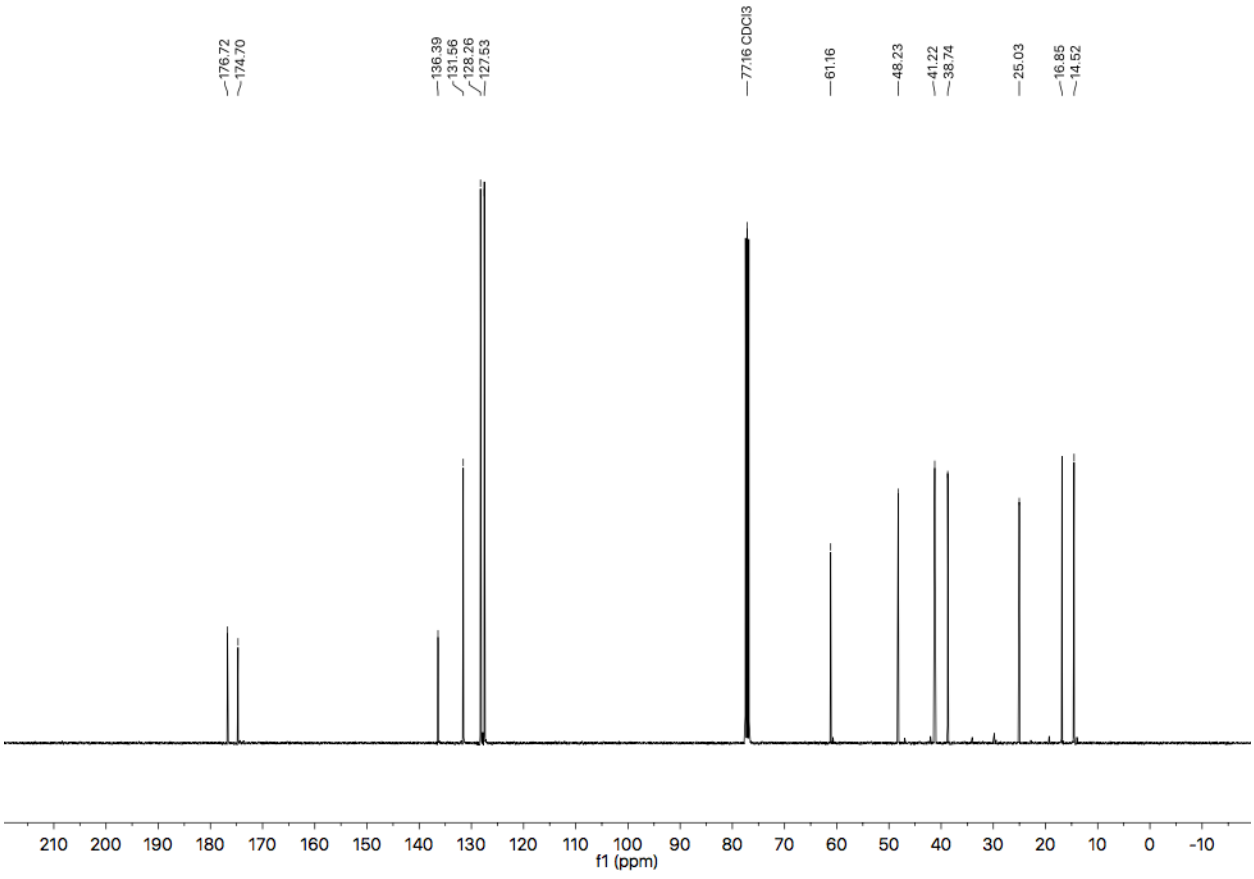
^{13}C NMR (101 MHz, $CDCl_3$) of compound **10**.



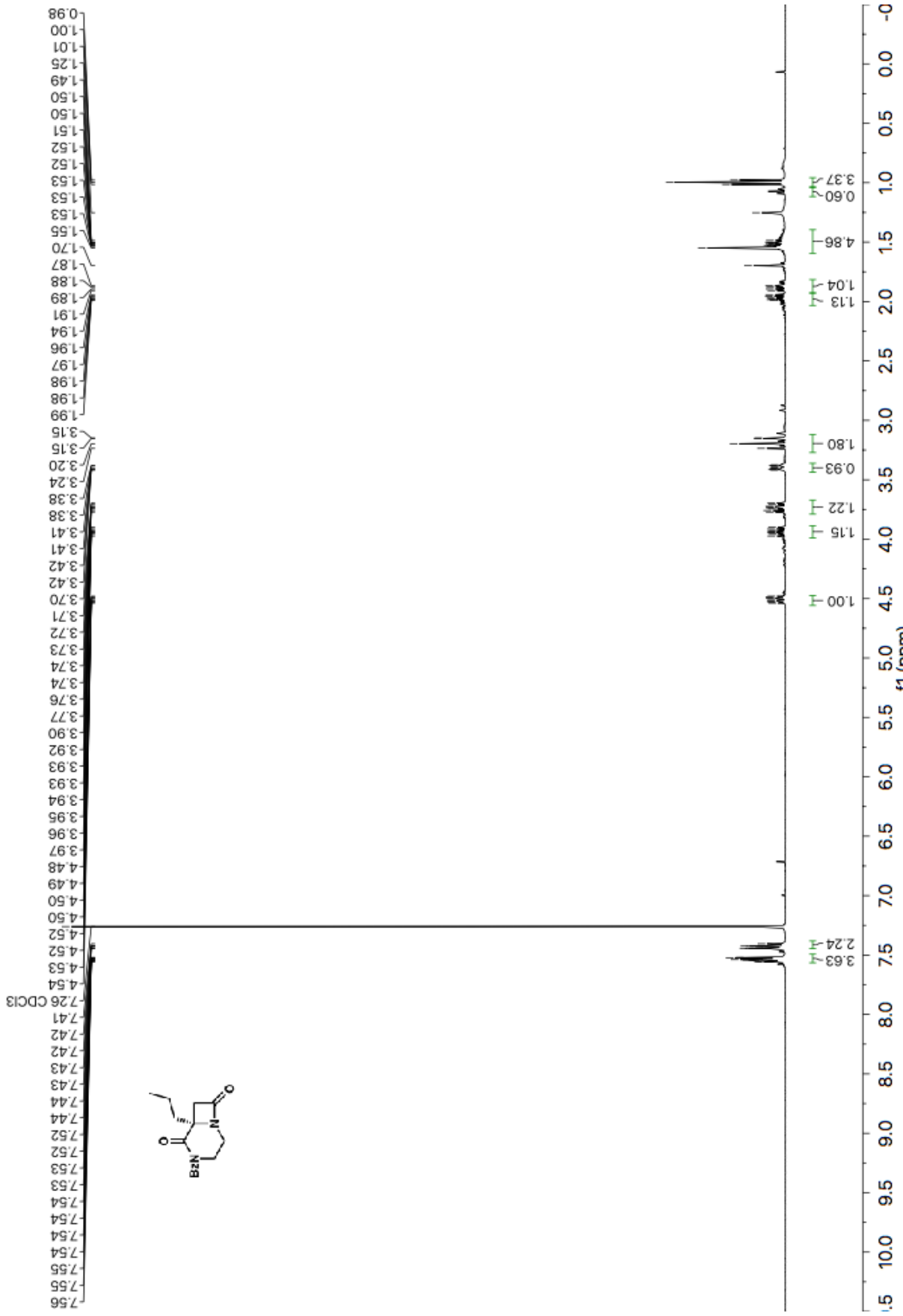
^{1}H NMR (400 MHz, $CDCl_3$) of compound **11.**



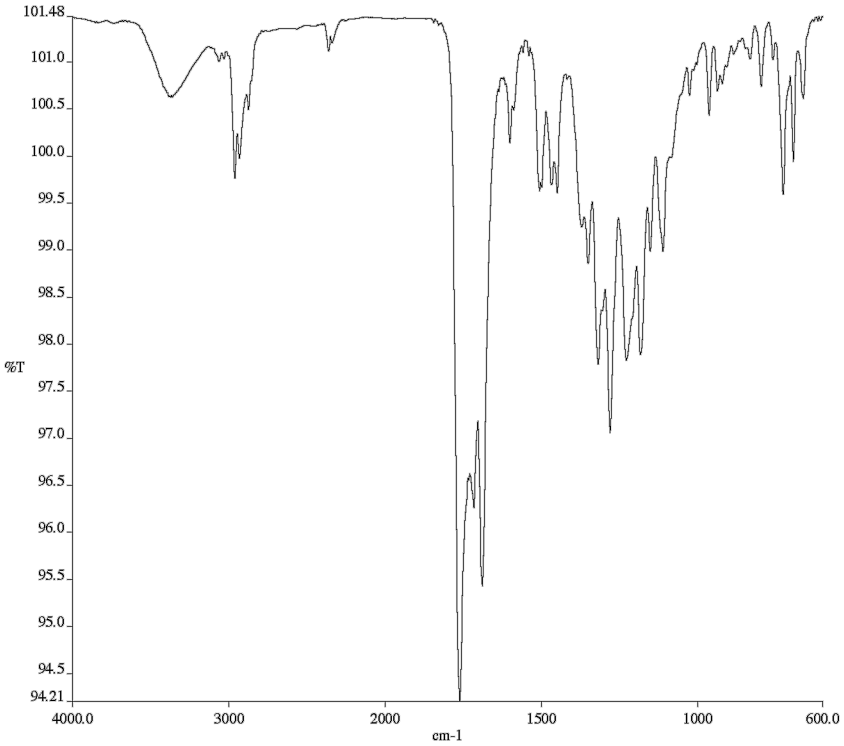
Infrared spectrum (Thin Film, NaCl) of compound **11**.



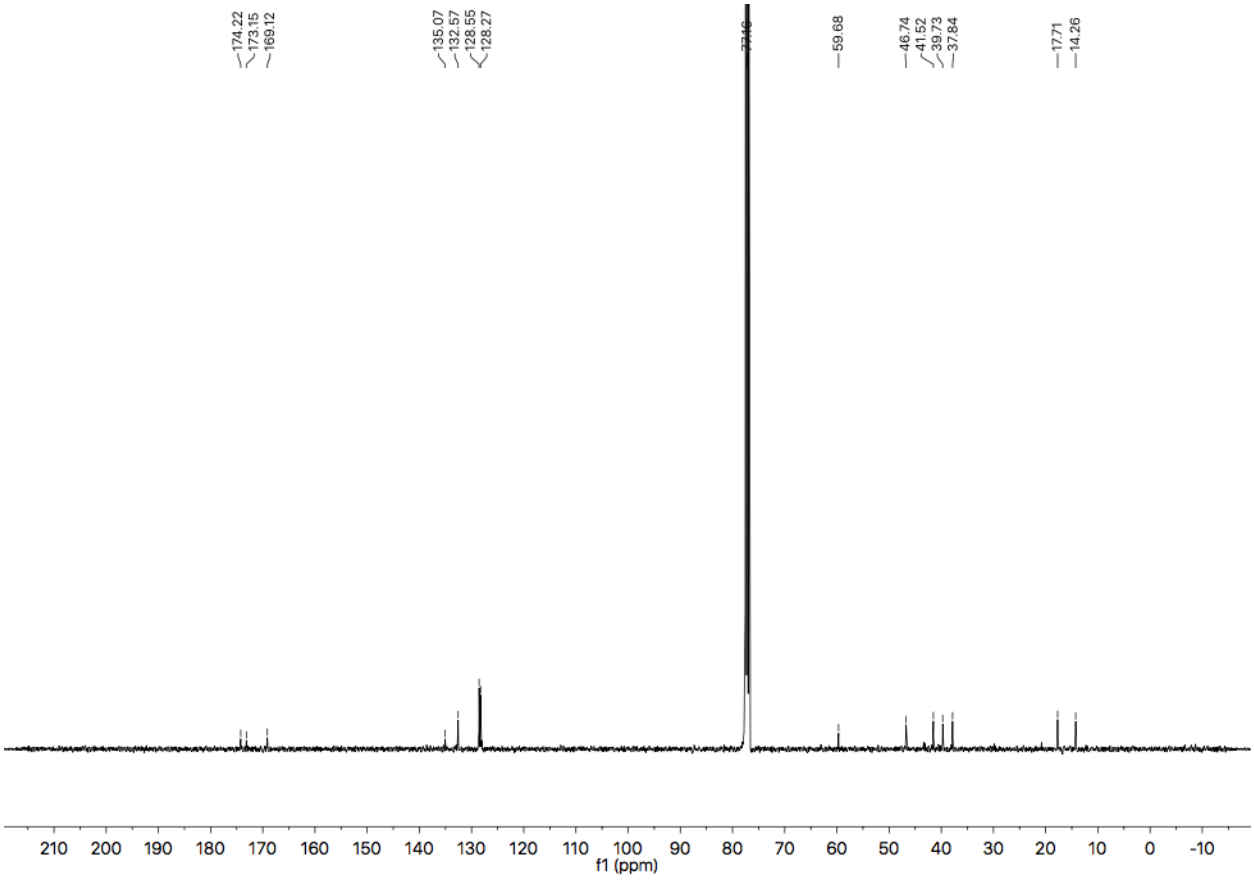
^{13}C NMR (101 MHz, $CDCl_3$) of compound **11**.



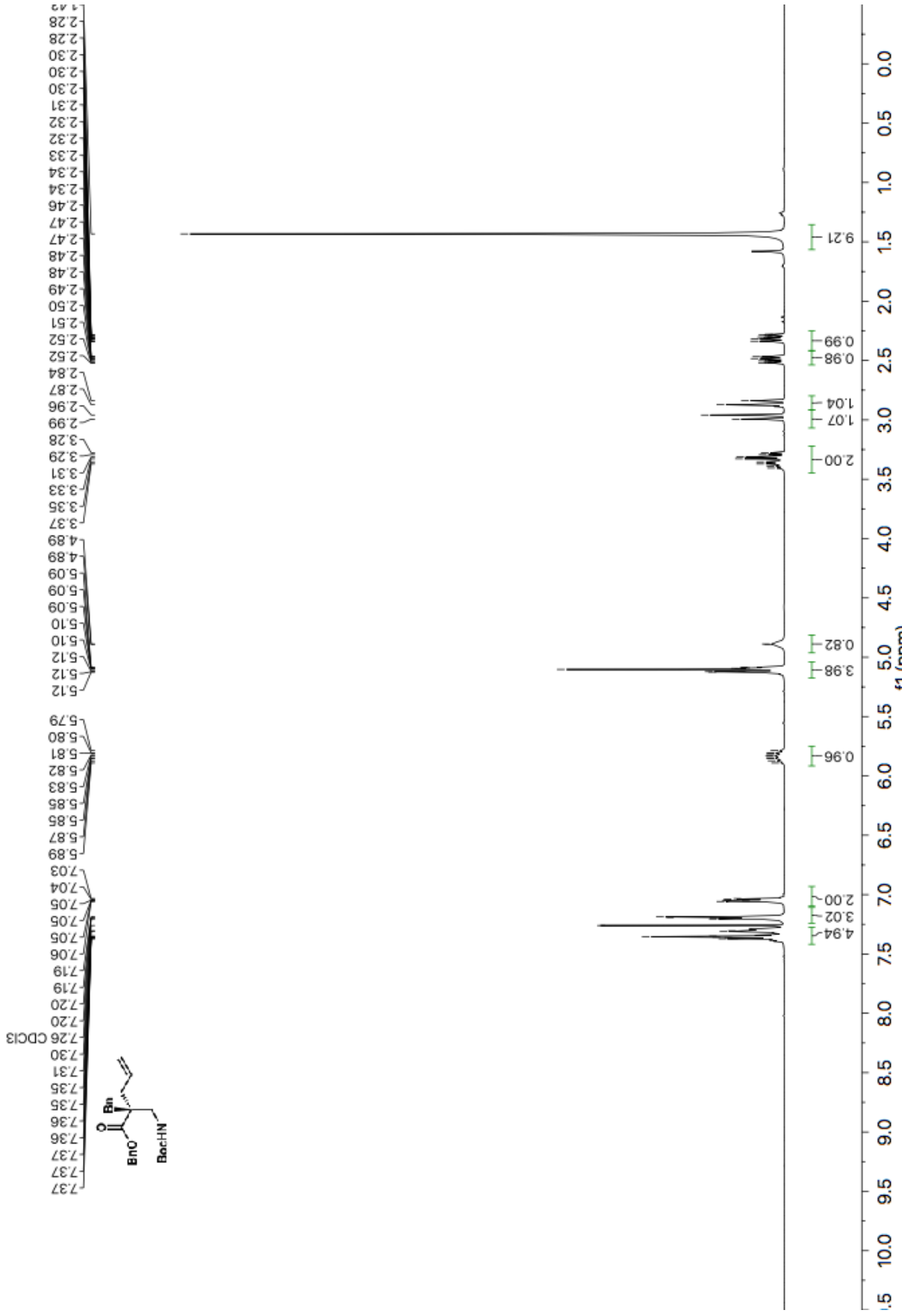
^{1}H NMR (400 MHz, $CDCl_3$) of compound **12.**



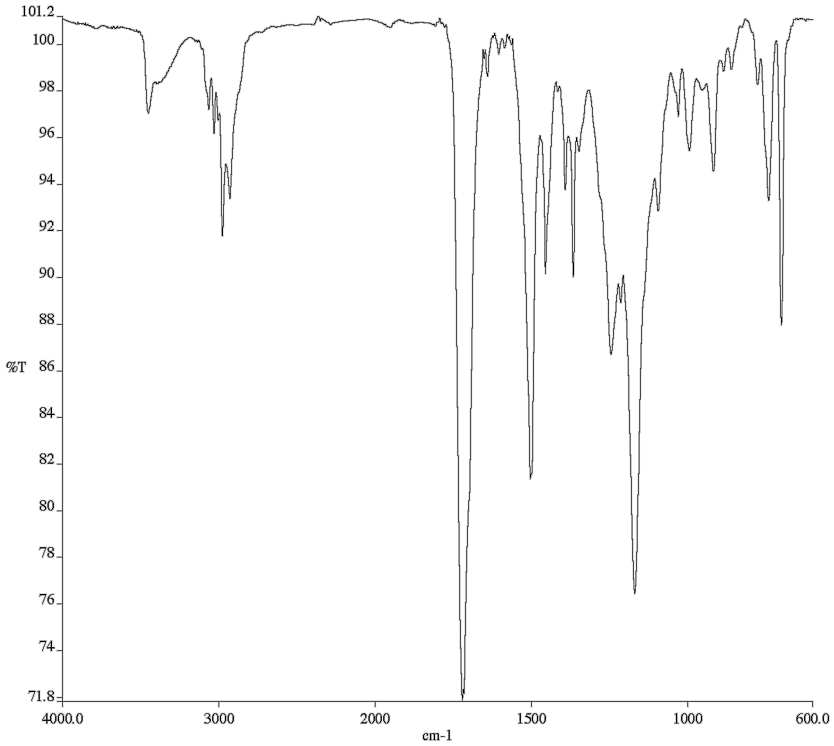
Infrared spectrum (Thin Film, NaCl) of compound **12**.



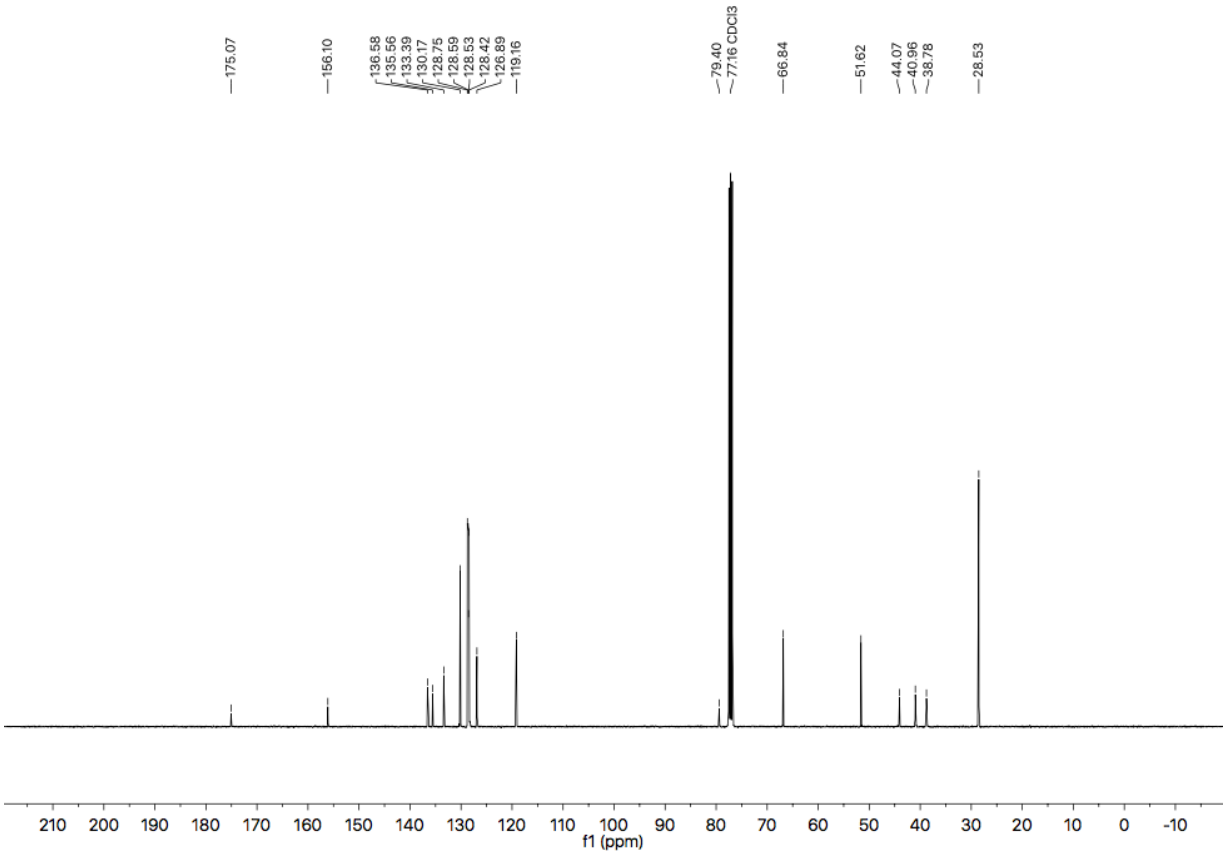
^{13}C NMR (101 MHz, $CDCl_3$) of compound **12**.



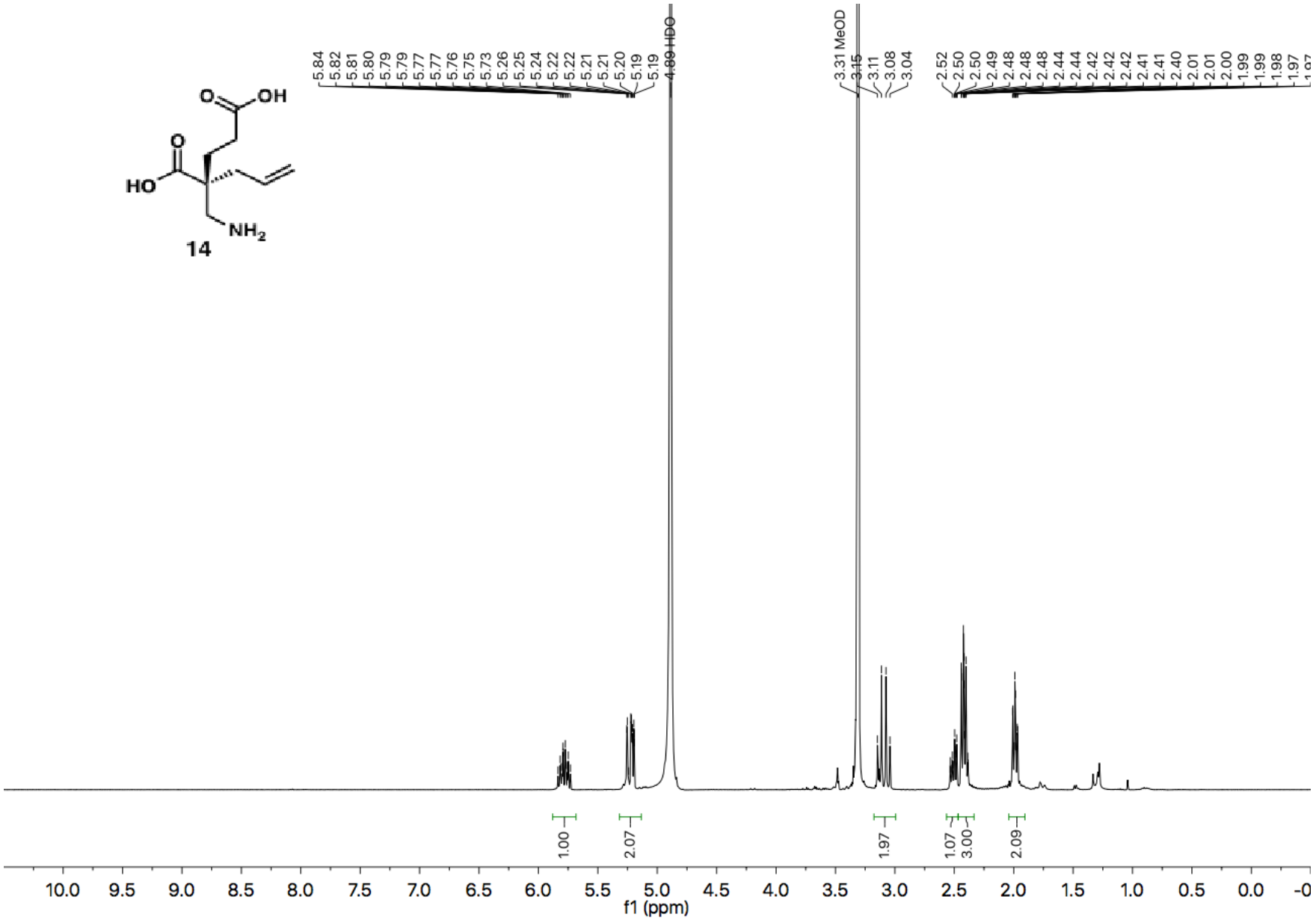
^{1}H NMR (400 MHz, $CDCl_3$) of compound **13.**



Infrared spectrum (Thin Film, NaCl) of compound **13**.

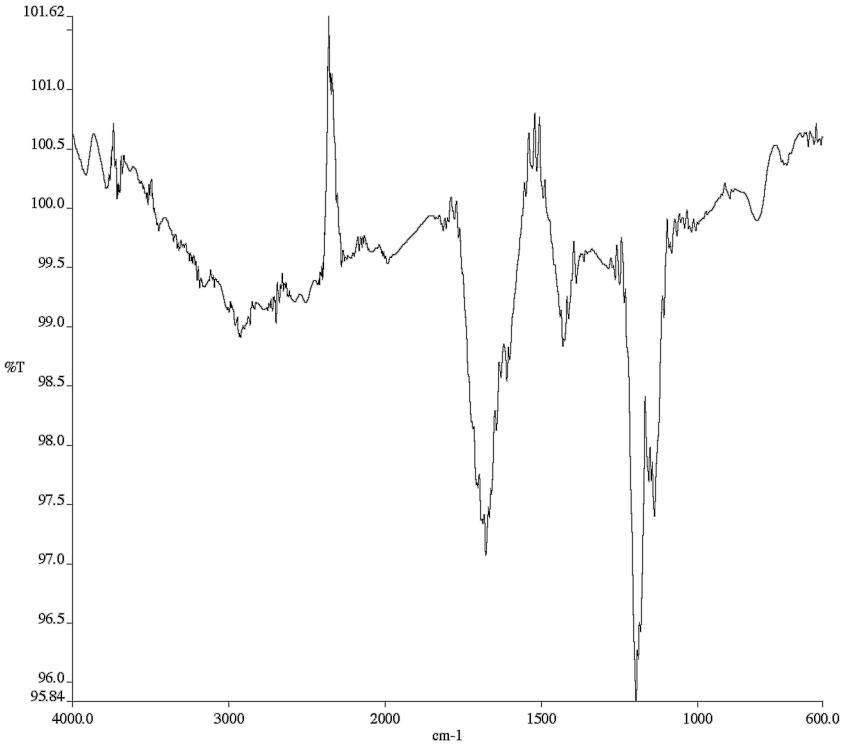


^{13}C NMR (101 MHz, $CDCl_3$) of compound **13**.

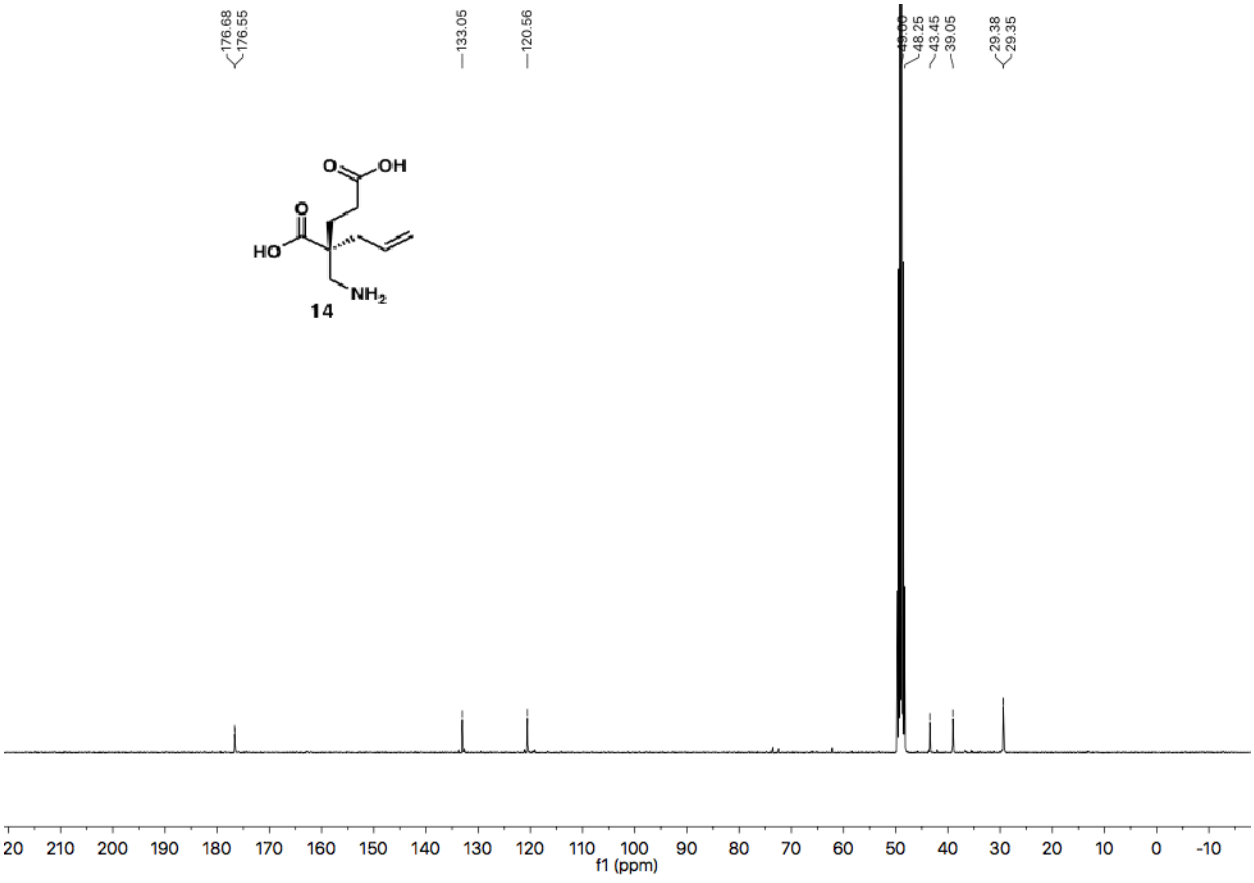


144

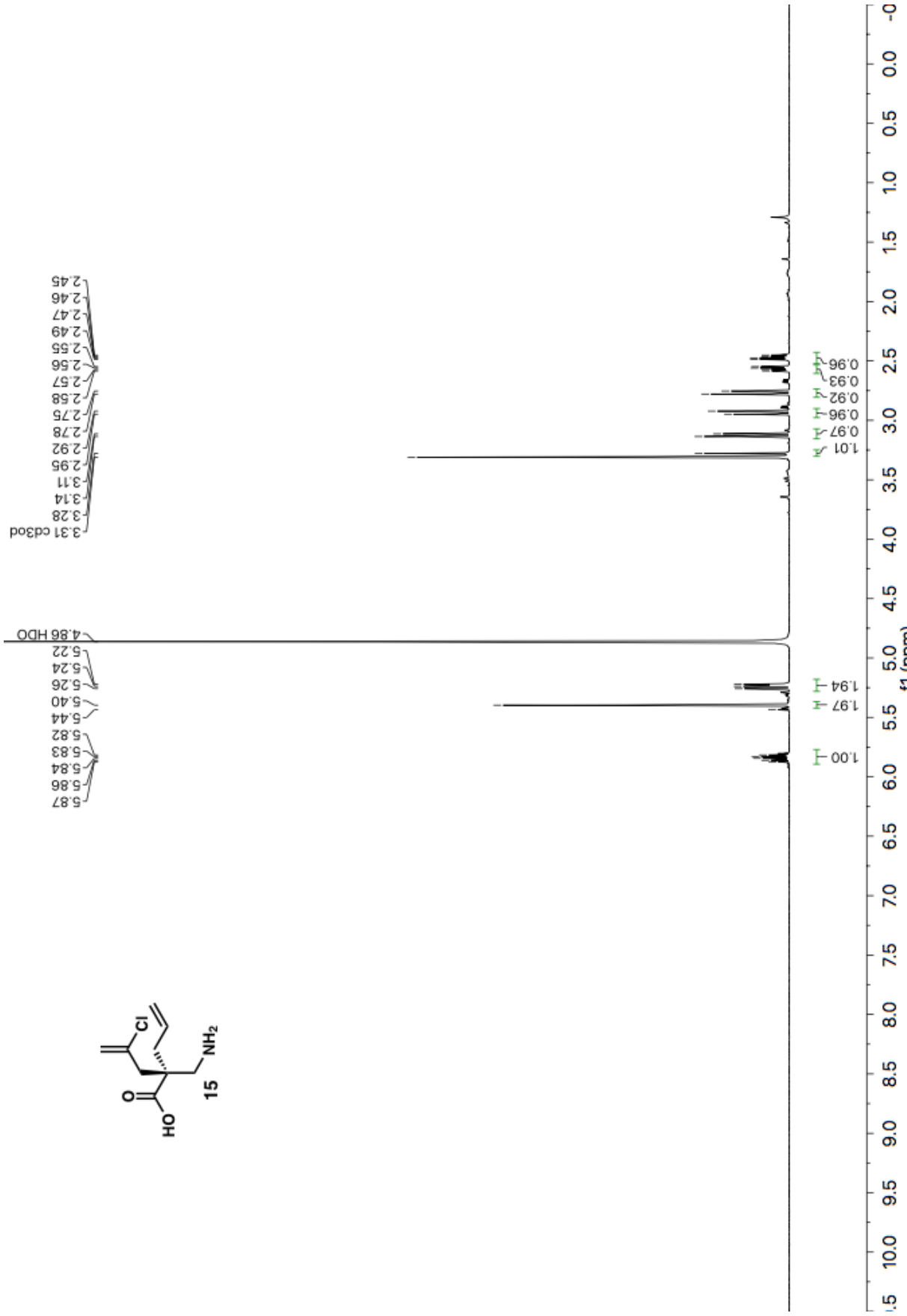
^{1}H NMR (400 MHz, CD_3OD) of compound **14.**



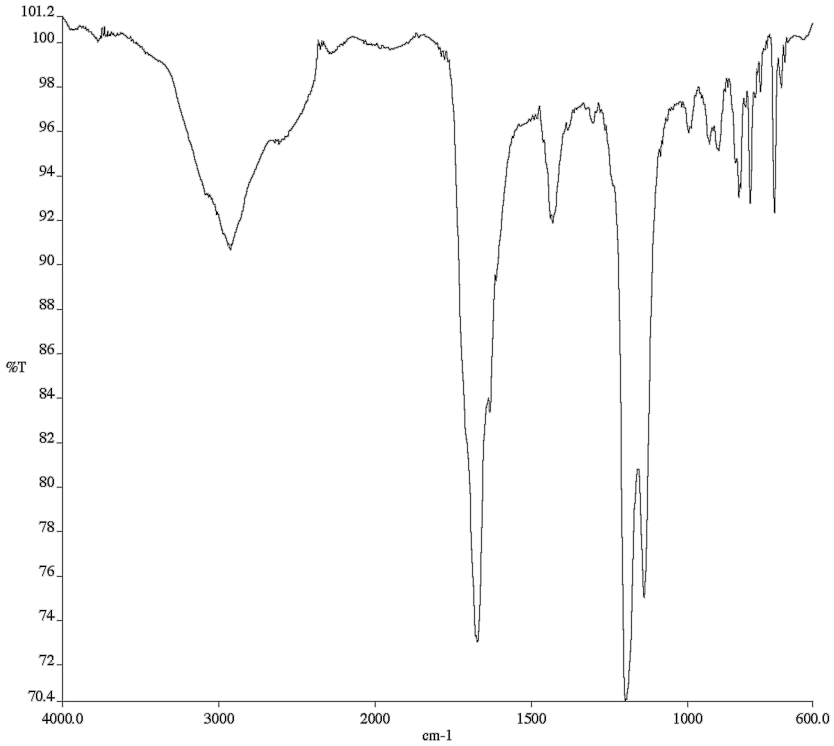
Infrared spectrum (Thin Film, NaCl) of compound **14**.



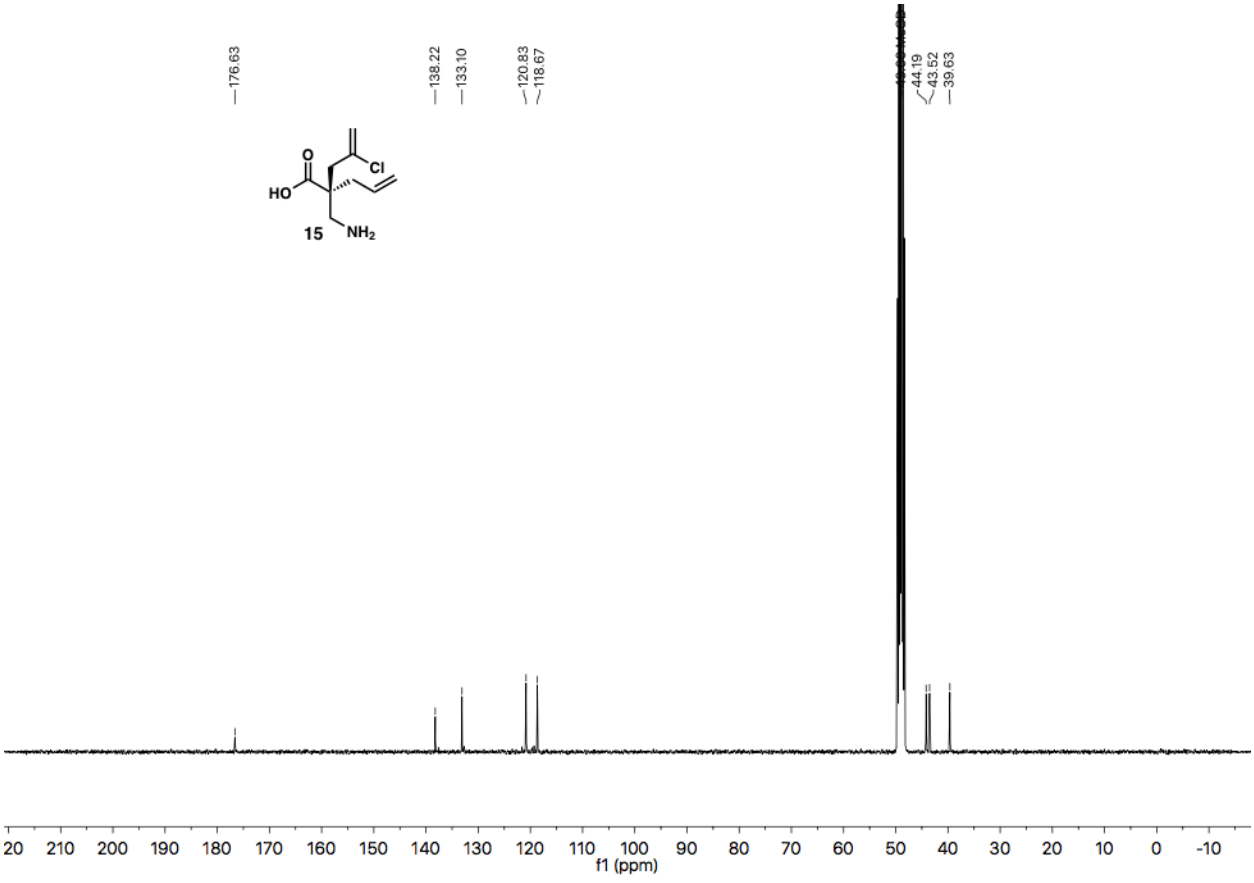
^{13}C NMR (101 MHz, CD_3OD) of compound **14**.



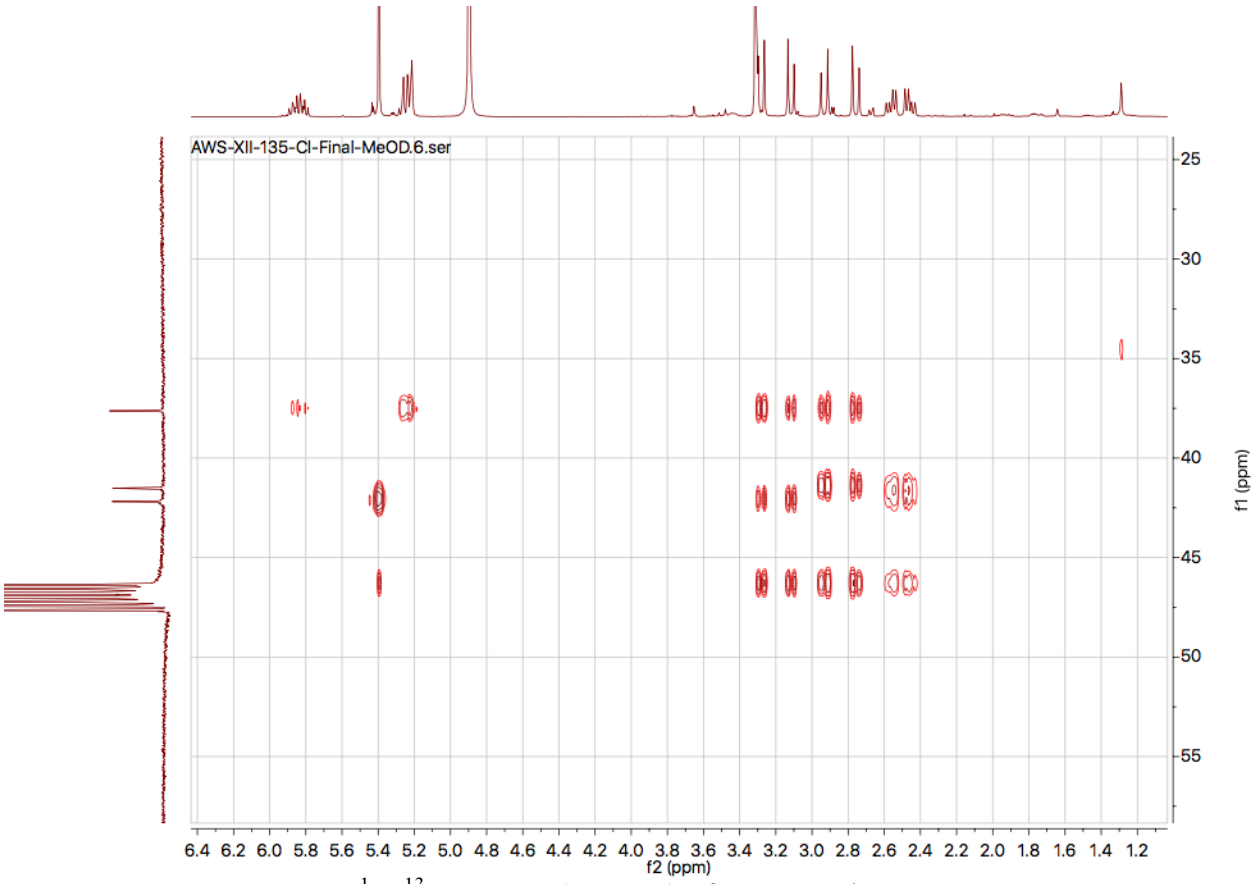
^{1}H NMR (600 MHz, CD_3OD) of compound **15.**



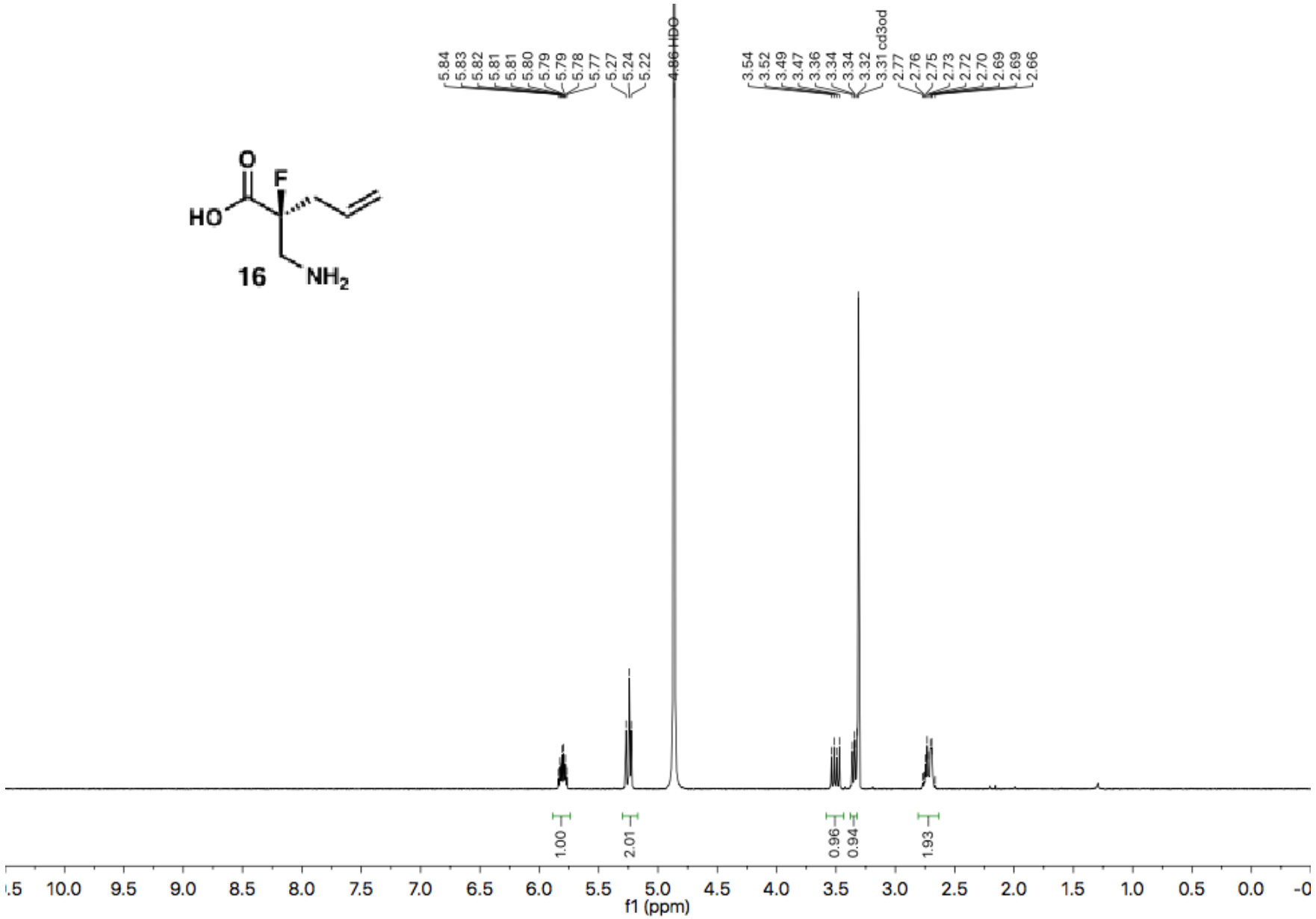
Infrared spectrum (Thin Film, NaCl) of compound **15**.



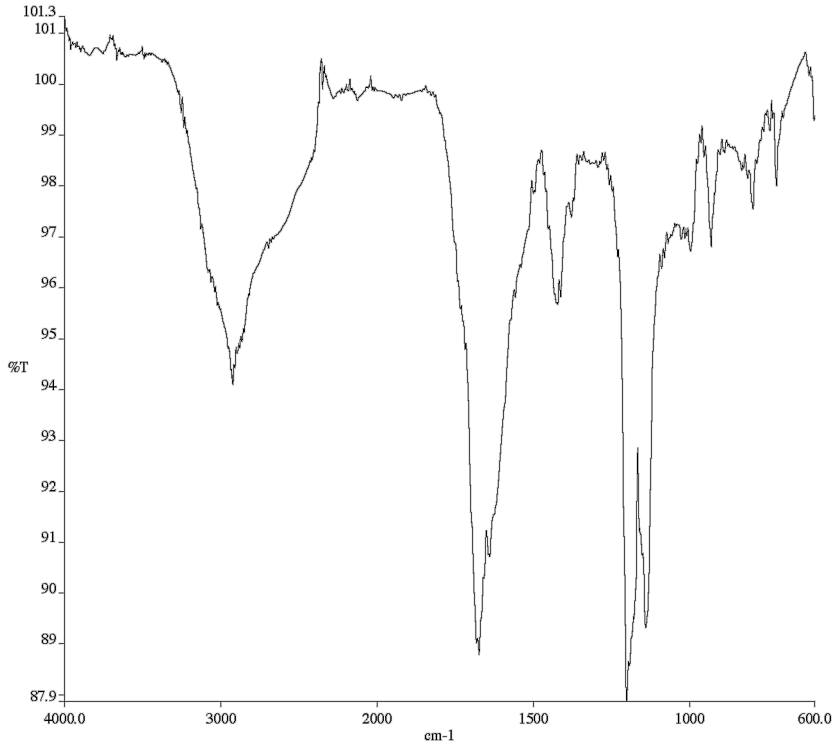
^{13}C NMR (101 MHz, CD_3OD) of compound **15**.



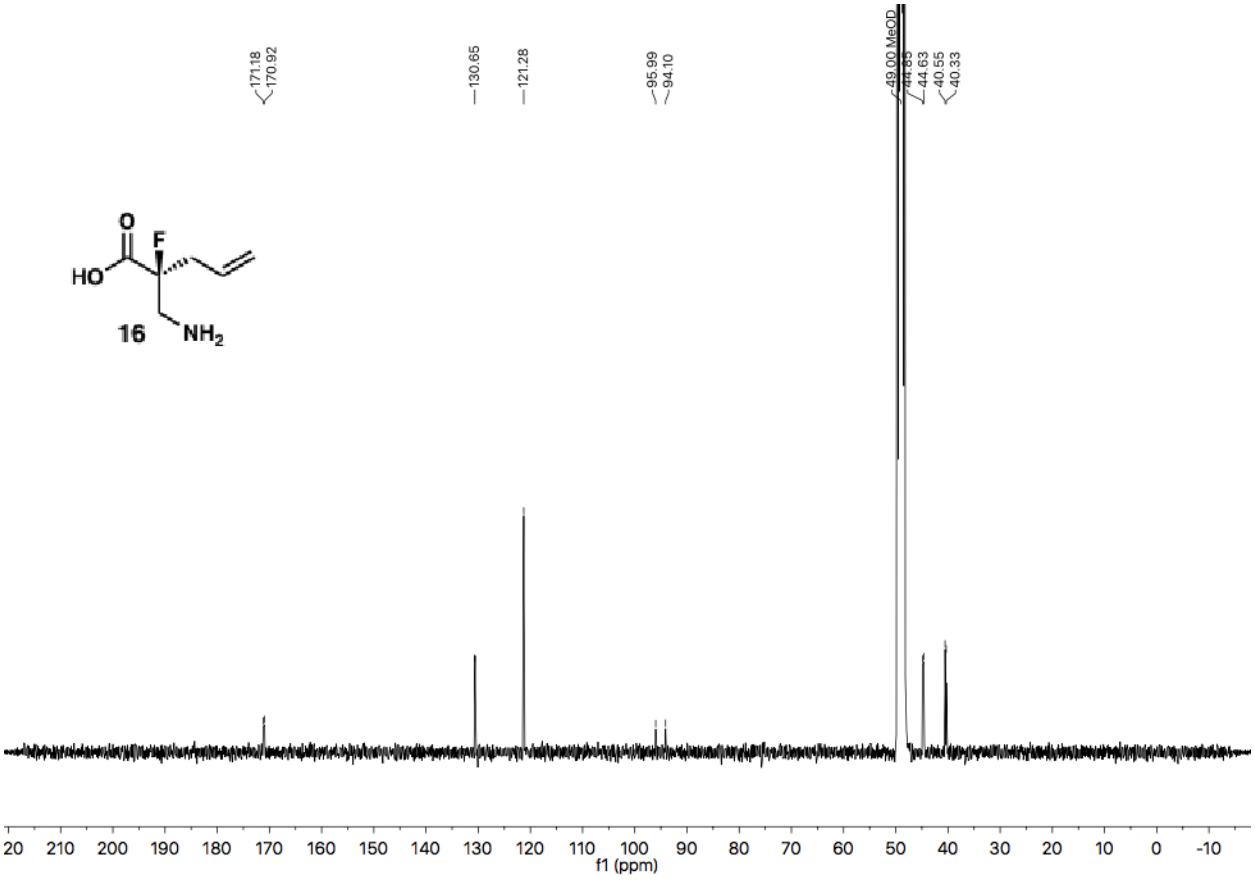
^{1}H-^{13}C HMBC (CD_3OD) of compound **15**



^{1}H NMR (600 MHz, CD_3OD) of compound **16.**

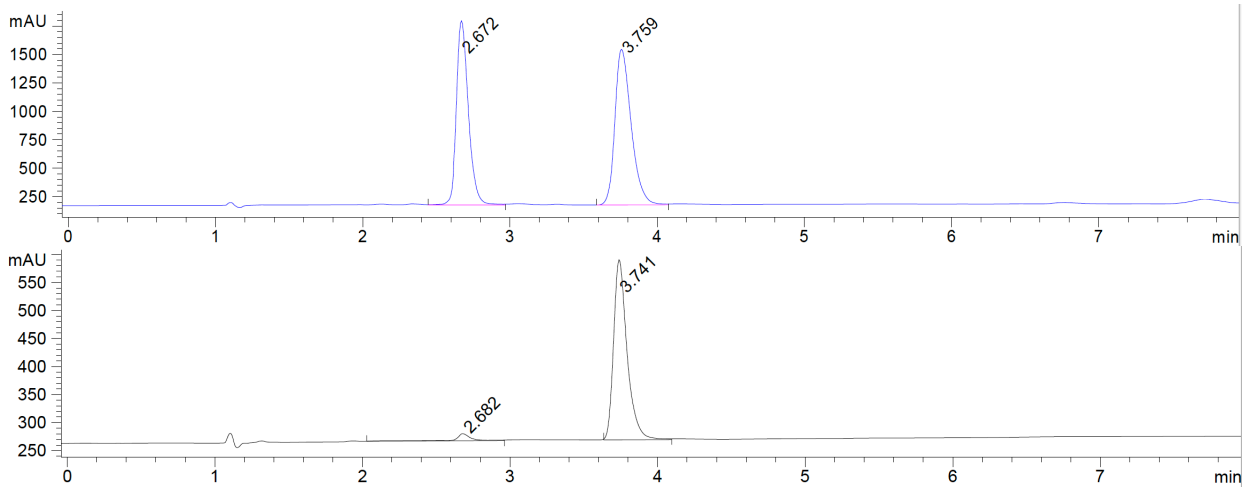


Infrared spectrum (Thin Film, NaCl) of compound **16**.



^{13}C NMR (101 MHz, CD_3OD) of compound **16**.

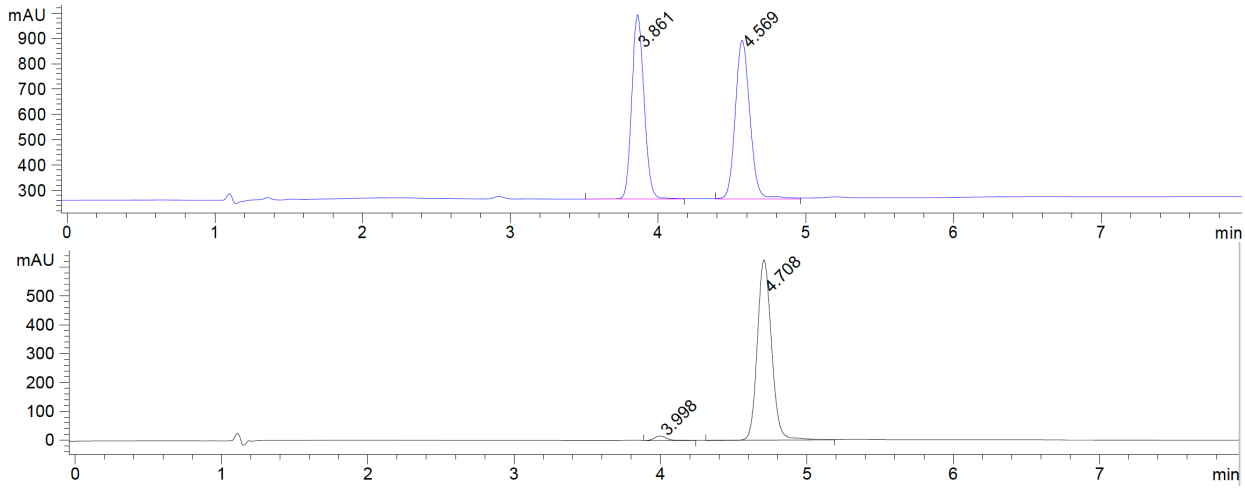
(4a)



Signal 1: DAD1 A, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.682	BB	0.1074	93.84398	12.52761	4.3842
2	3.741	BB	0.0985	2046.66162	320.50800	95.6158

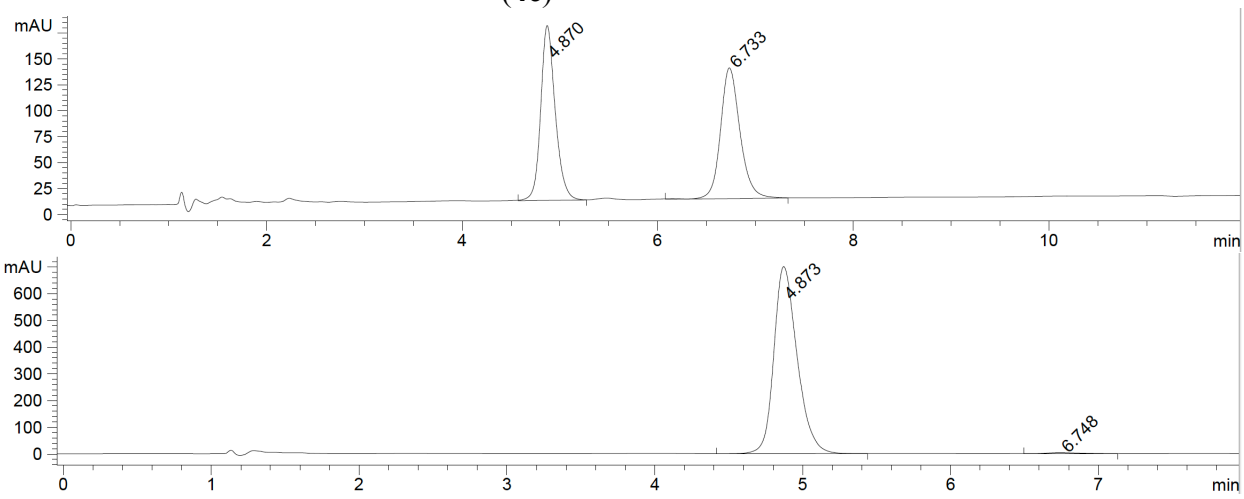
(4b)



Signal 1: DAD1 A, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.998	VB	0.0908	88.14365	15.40434	2.0432
2	4.708	BB	0.1070	4225.88428	623.91833	97.9568

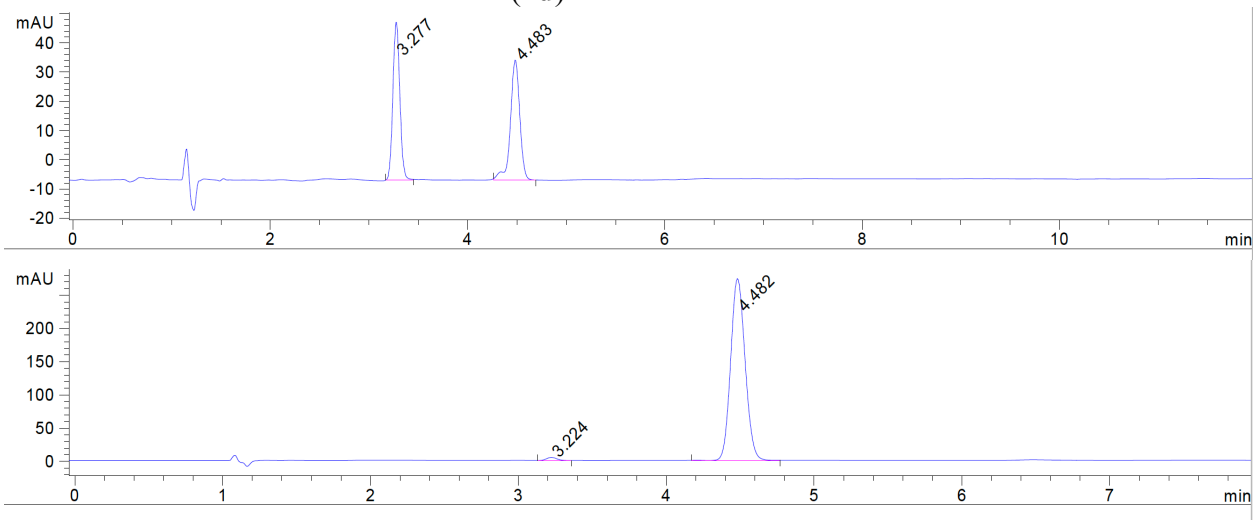
(4c)



Signal 1: DAD1 A, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.873	VB	0.1680	7679.94434	700.18347	99.2972
2	6.748	BB	0.2133	54.35474	3.93044	0.7028

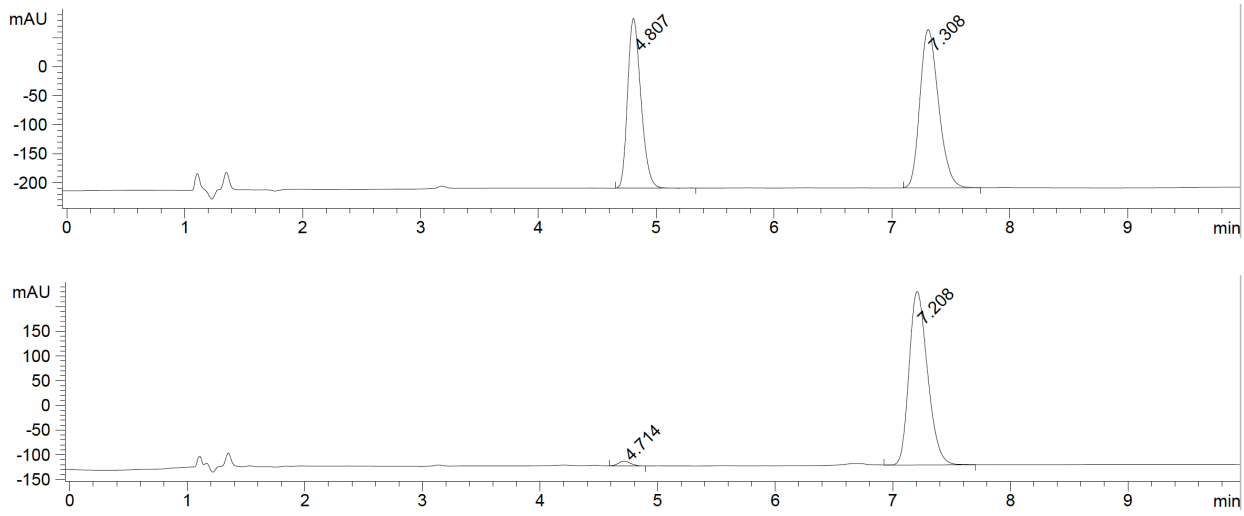
(4d)



Signal 2: DAD1 D, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.224	BB	0.0779	23.15616	4.66227	1.2282
2	4.482	BB	0.1076	1862.22693	273.07532	98.7718

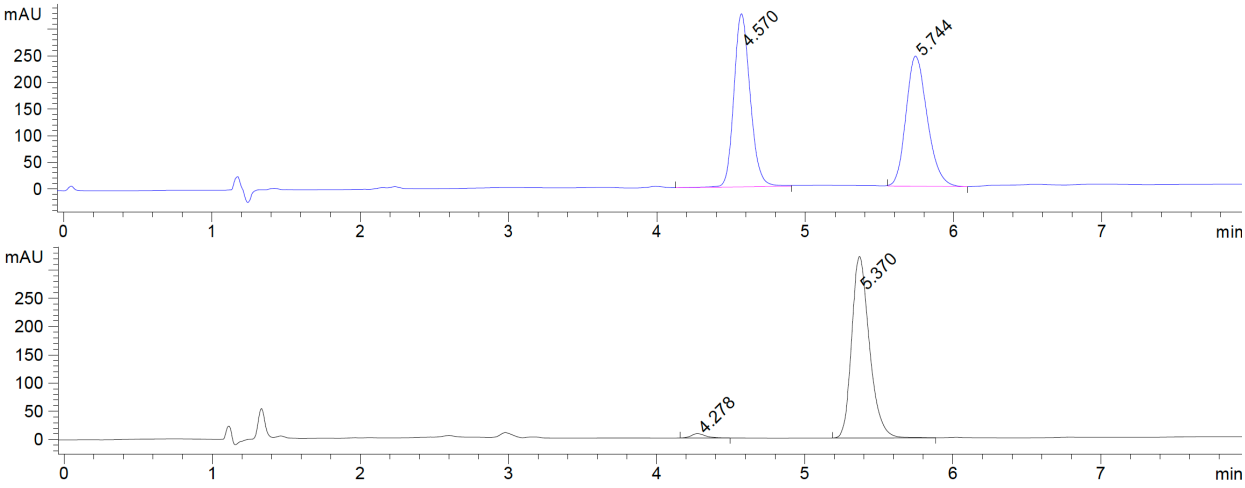
(4e)



Signal 1: DAD1 A, Sig=210,8 Ref=360,100

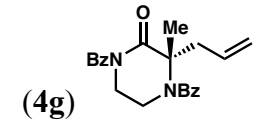
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.714	VV	0.1128	71.75687	9.87509	1.8279
2	7.208	VB	0.1720	3853.88745	351.23074	98.1721

(4f)

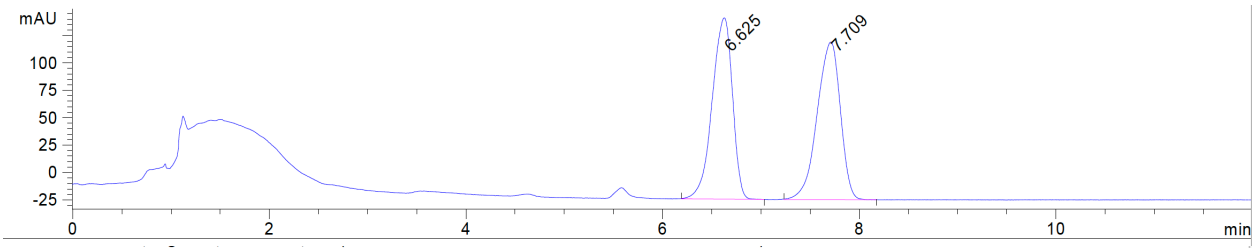


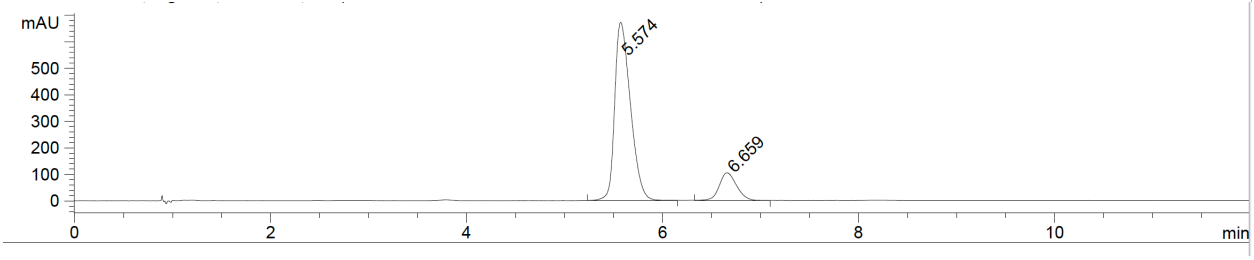
Signal 1: DAD1 A, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.278	BB	0.1077	56.59460	7.88515	2.0657
2	5.370	BB	0.1297	2683.07373	320.43164	97.9343



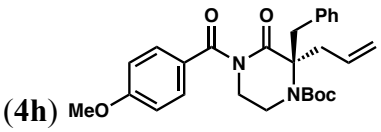
(4g)



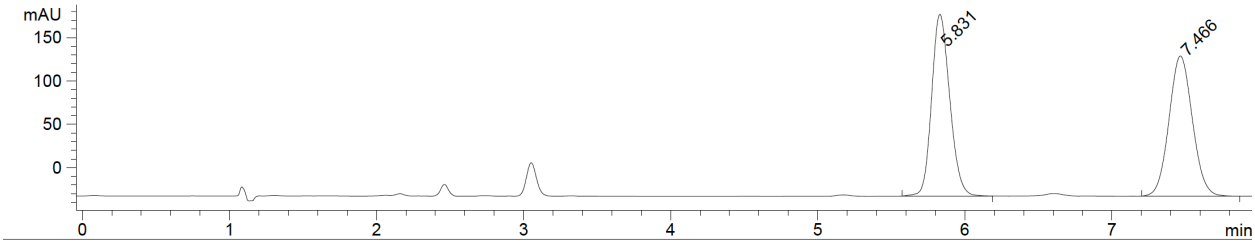


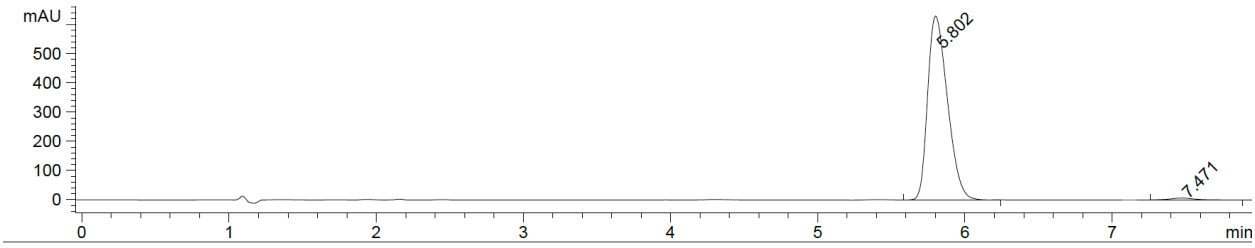
Signal 4: DAD1 D, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.574	BB	0.1751	7531.16260	670.04437	85.2476
2	6.659	BB	0.1893	1303.29749	104.62668	14.7524



(4h)

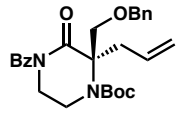


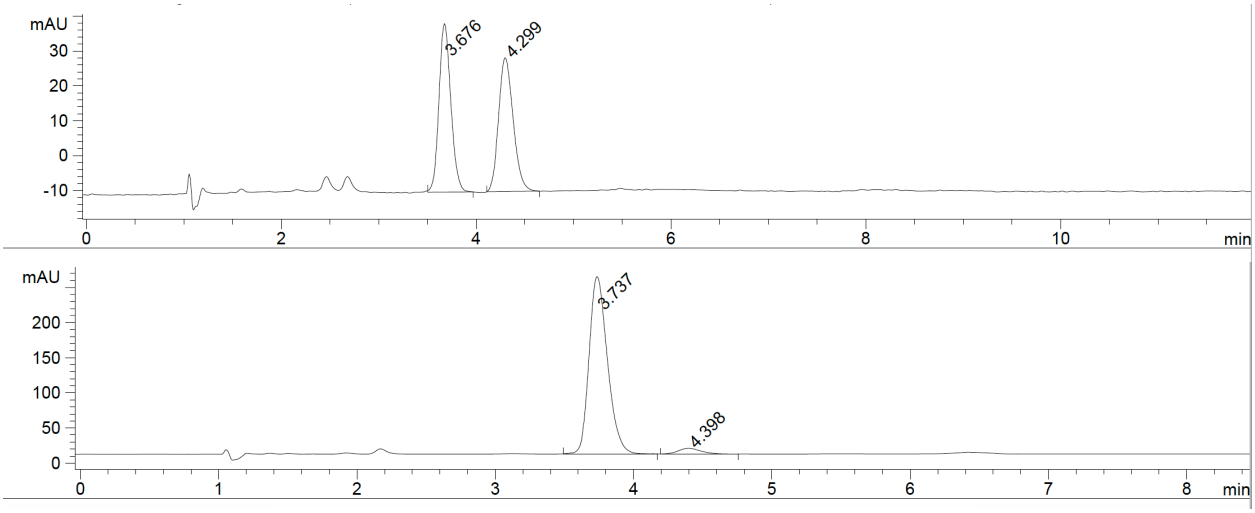


Signal 2: DAD1 D, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.802	VB	0.1454	5901.30762	629.22693	98.6699
2	7.471	BB	0.1811	79.55283	6.77095	1.3301

(**4i**):

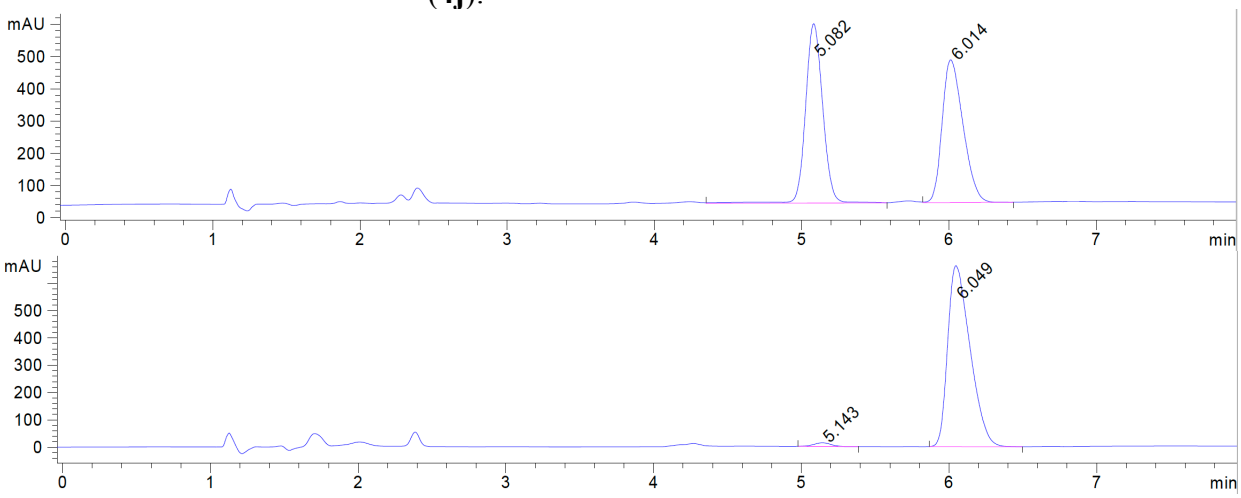




Signal 3: DAD1 D, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.737	BB	0.1401	2339.33643	252.43327	96.1496
2	4.398	BB	0.1769	93.68114	8.22145	3.8504

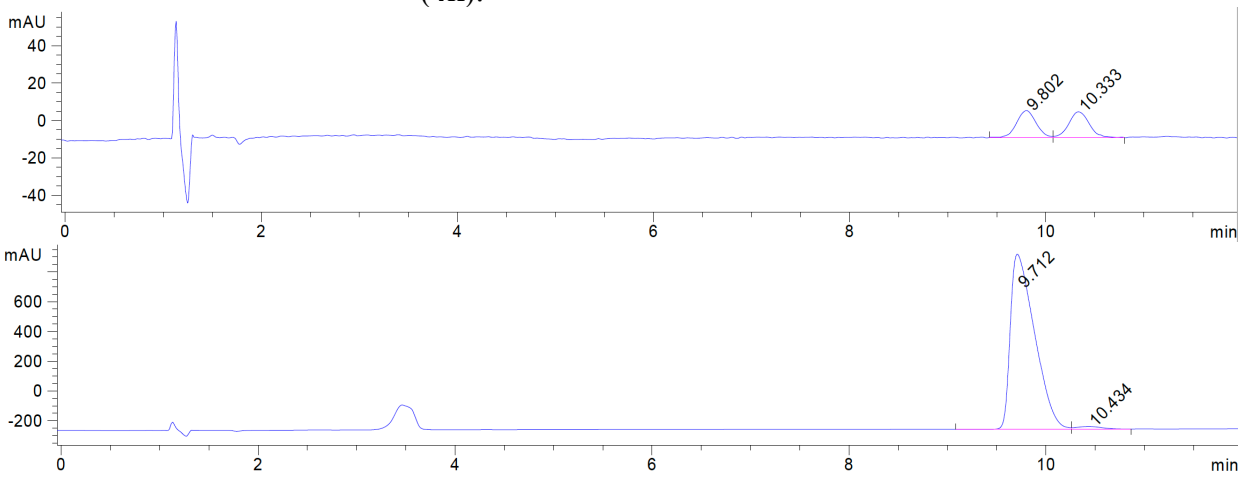
(4j):



Signal 1: DAD1 A, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.143	BB	0.1238	106.17220	13.49768	1.4991
2	6.049	BV	0.1632	6976.36621	660.80591	98.5009

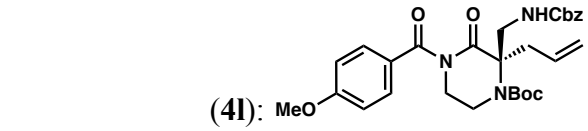
(4k):

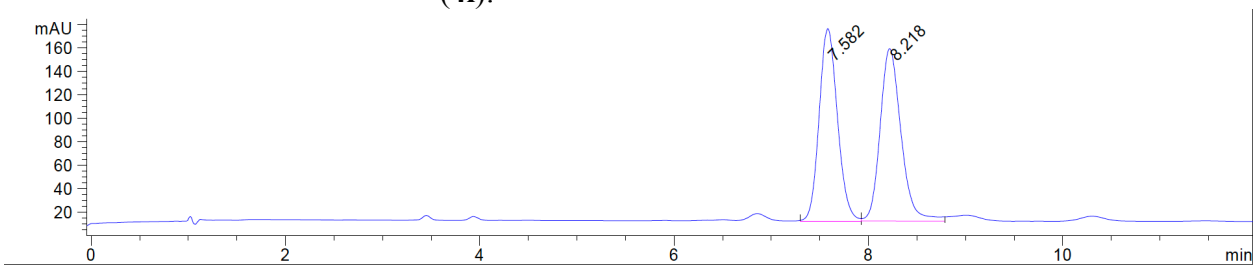


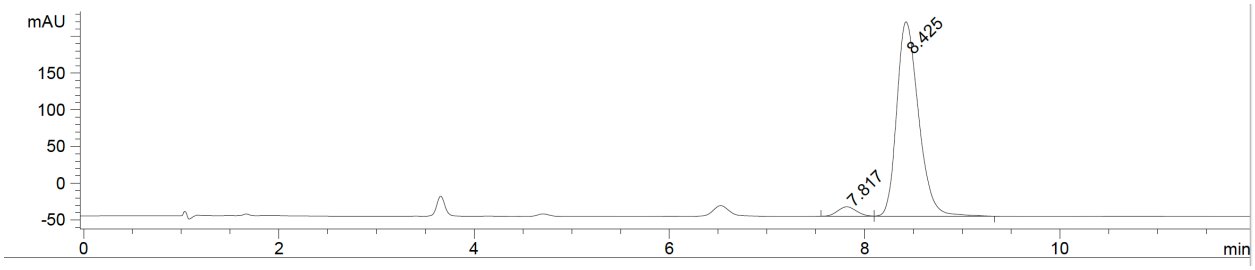
Signal 2: DAD1 B, Sig=235,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.712	BV	0.2501	1.22217e4	734.53900	98.5481
2	10.432	VB	0.2762	180.06230	10.28922	1.4519

(**4l**):



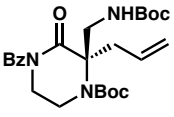


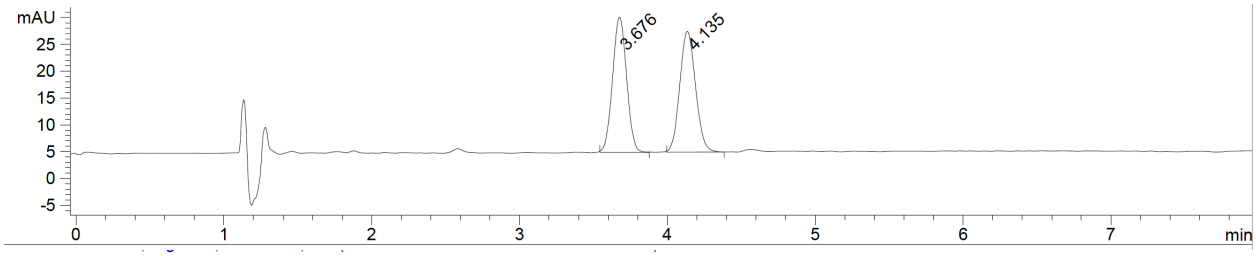


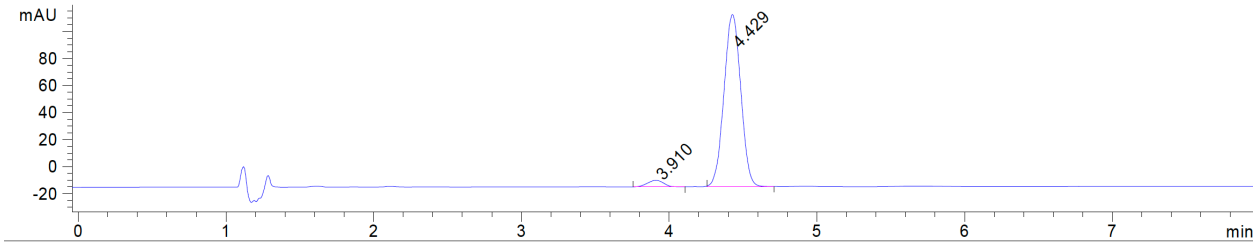
Signal 5: DAD1 E, Sig=280,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.817	BV	0.2110	179.22209	13.15129	4.1507
2	8.425	VB	0.2423	4138.61084	264.92801	95.8493

(**4m**)



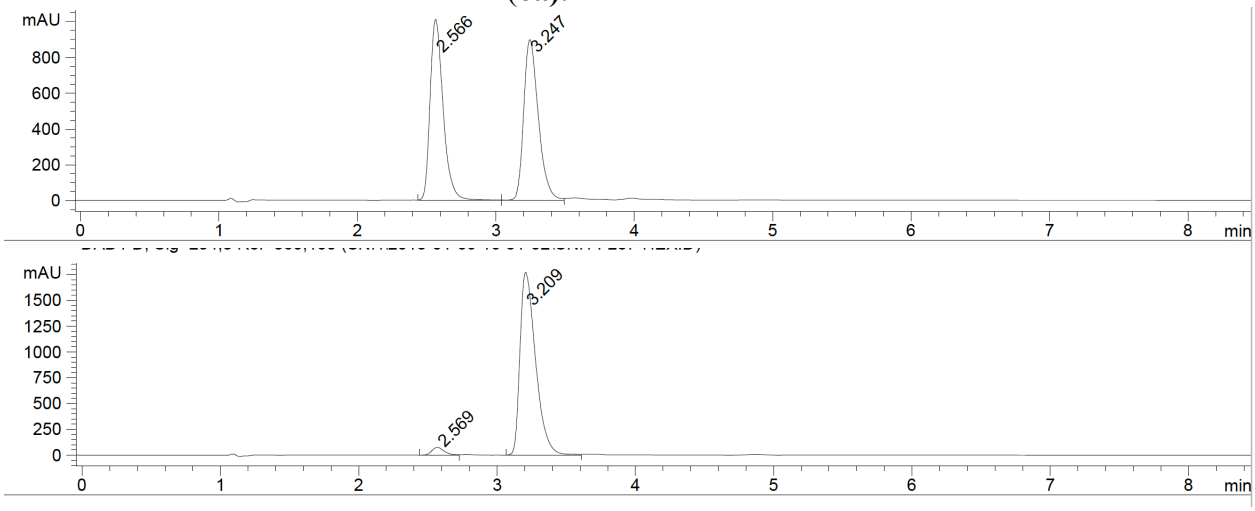




Signal 2: DAD1 D, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.910	BB	0.1151	36.57735	4.89780	3.4904
2	4.429	BB	0.1288	1011.37030	127.21075	96.5096

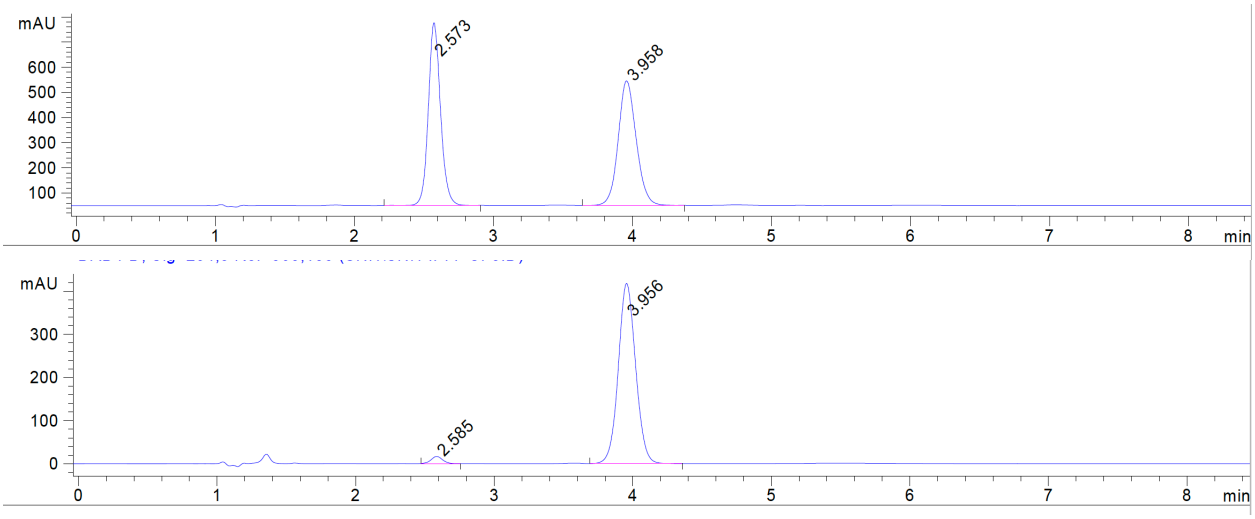
(6a):



Signal 3: DAD1 D, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.569	BV	0.0968	465.80981	74.64001	3.2381
2	3.209	BV	0.1202	1.39195e4	1761.90564	96.7619

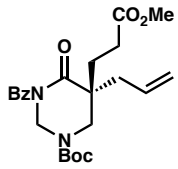
(6b):

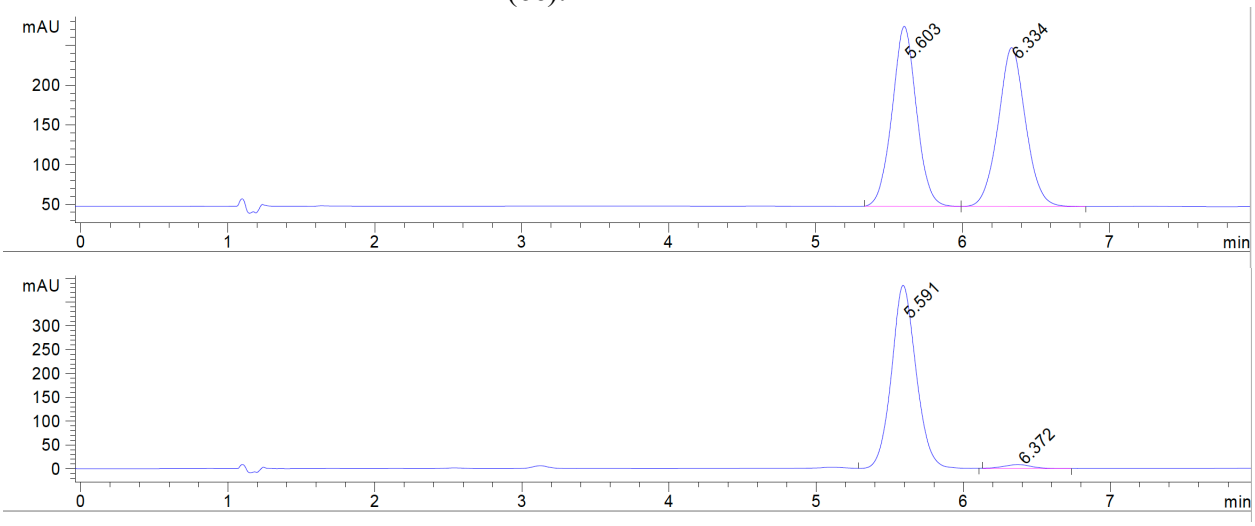


Signal 3: DAD1 D, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.585	BB	0.0883	97.37040	16.64309	2.6055
2	3.956	VB	0.1378	3639.69214	417.14053	97.3945

(**6c**):

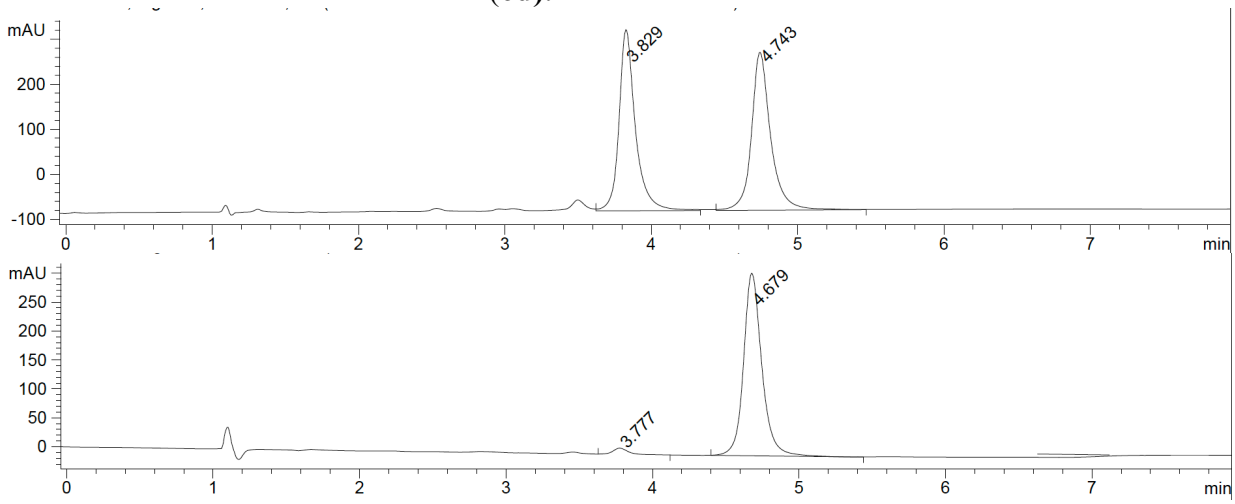




Signal 2: DAD1 D, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.591	VB	0.1759	4477.78711	384.37347	97.5668
2	6.372	BB	0.2031	111.66913	8.40213	2.4332

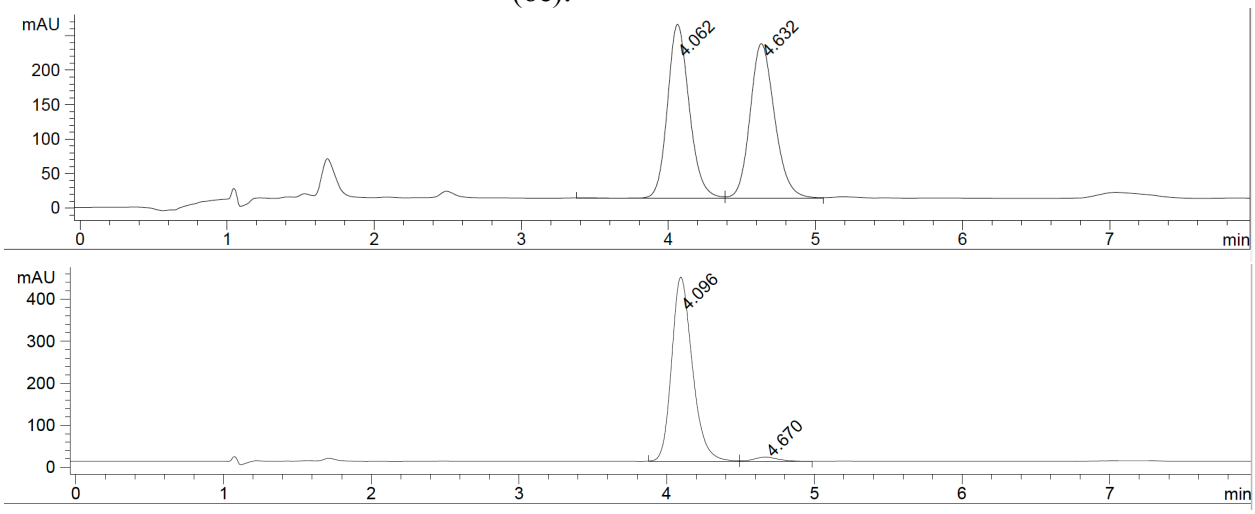
(**6d**):



Signal 1: DAD1 A, Sig=210,8 Ref=360,100

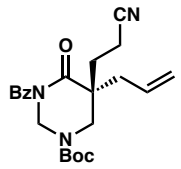
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.777	VB	0.1044	73.38116	10.65119	2.6015
2	4.679	BB	0.1298	2747.39282	314.87576	97.3985

(**6e**):

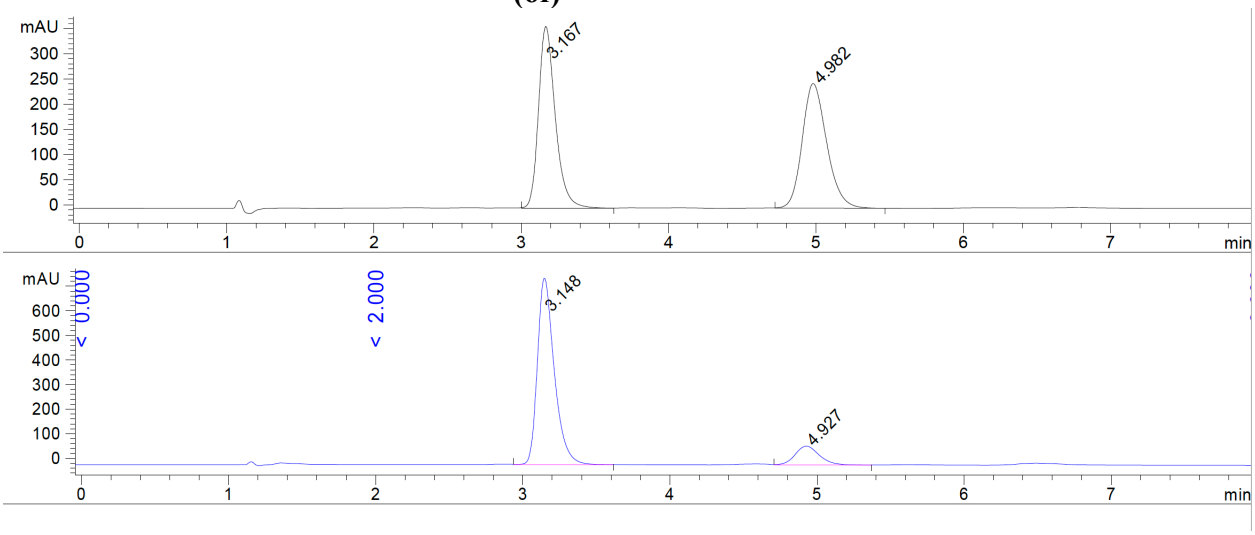


Signal 2: DAD1 D, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.096	BV	0.1500	4277.13281	437.67798	97.5212
2	4.670	VB	0.1667	108.71631	10.00878	2.4788

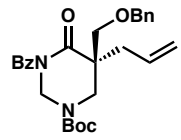


(6f)

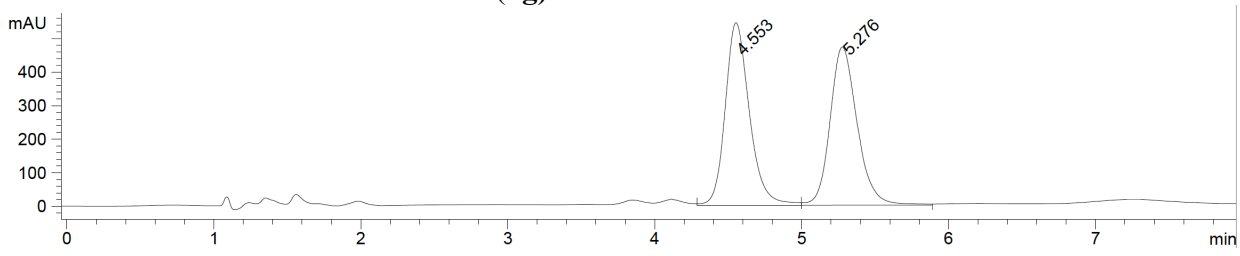


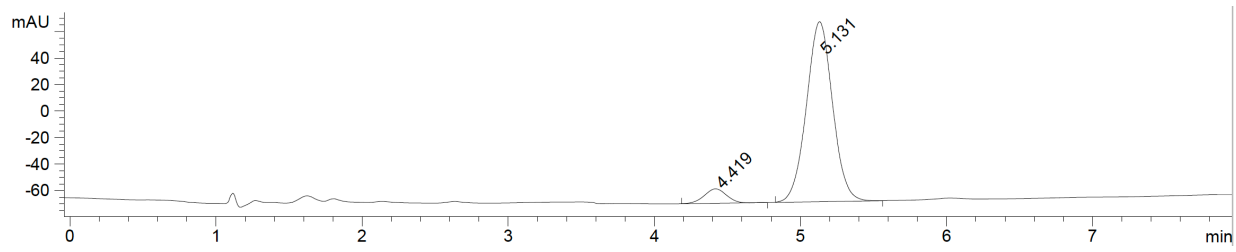
Signal 2: DAD1 D, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.148	VB	0.1213	6056.08936	757.35760	87.2243
2	4.927	VB	0.1749	887.03571	76.73595	12.7757



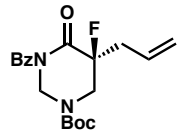
(6g)



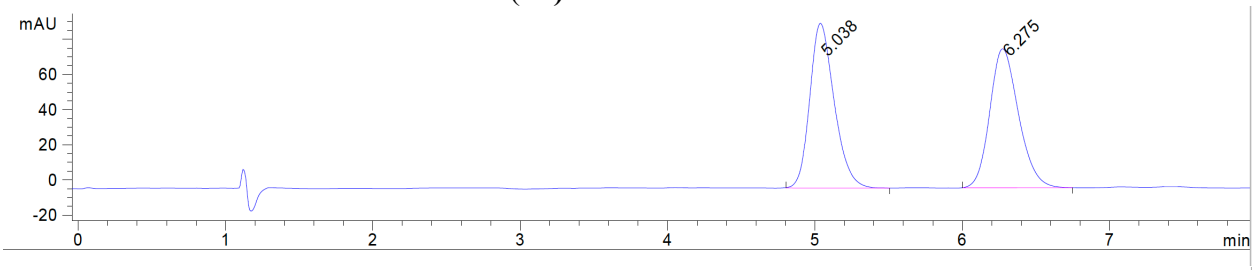


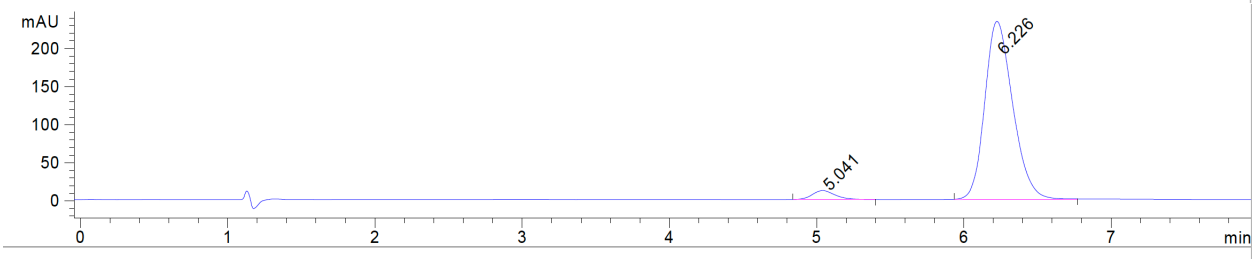
Signal 1: DAD1 A, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.419	BB	0.1631	114.48997	10.84806	6.3355
2	5.131	BB	0.1934	1692.62048	135.80150	93.6645



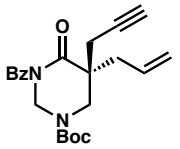
(6h)



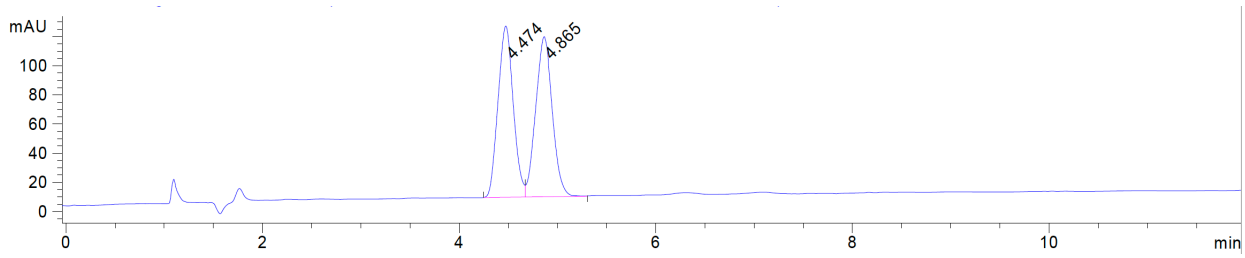


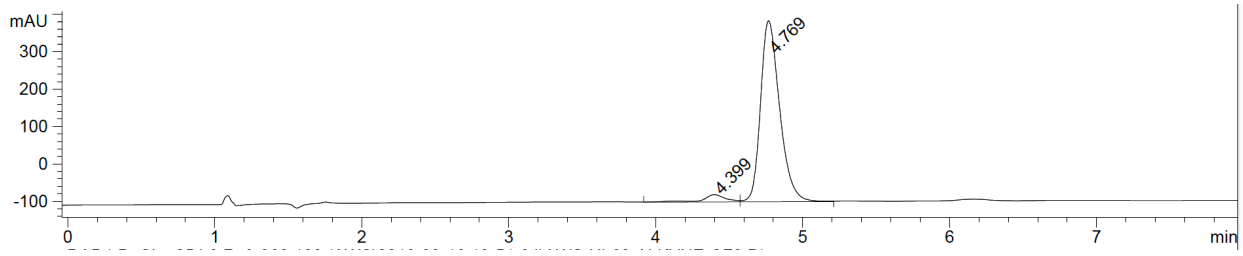
Signal 2: DAD1 D, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.041	BB	0.1631	123.06105	11.66360	3.8358
2	6.226	BB	0.2062	3085.13306	233.49387	96.1642



(6i)





Signal 1: DAD1 A, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.399	VV	0.1573	218.63586	19.73255	4.7548
2	4.769	VB	0.1418	4379.61133	482.85495	95.2452